ENDOCRINE THERAPY
IN
GENERAL PRACTICE

THE GENERAL PRACTICE MANUALS

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(OTHER TITLES IN PREPARATION)



Endocrine Therapy in General Practice

By

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Psychiatry and Endocrinology



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To the Memory of

EDWIN A SEVRINGHAUS, M D

My Father

who began his practice of medicine at the time hormone therapy was begun, with oral use of thyroid, whose enthusiasm for endocrinology colors my earliest recollections of professional discussions with him and whose concern for his patients comfort continues to be a force in my clinical work.

First Edition September, 1938
Second Edition December 1938
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Fourth Edition Revised 1942
Fifth Edition Revised 1945
Reprinted April, 1946

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PREFACE TO THE FIFTH EDITION

The request for a revision of this volume serves to focus attention on a number of advances which have been achieved in the past three years The fundamental concepts of the author and the basic structure of the book have not seemed to require alteration Details have been brought up to date to accord with the recent publications from clinical endocrinologists, especially when experience has proved that genuine advances have been made Notably there are such advances as thiouracil therapy for thyrotoxicosis, the modification of insulin action in several ways, improvement of adrenal cortex extracts, and developments in the concepts of the gonadotrophic hormones The changes in the commercial preparations of hormones are incorporated It is hoped that the volume will continue to serve as a simple guide to reasonable use of endocrine materials in therapy

—ELMER L SEVRINGHAUS M D

Madison Wis July 2 1945

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PREFACE TO THE FIRST EDITION

To assist the physician who desires to prescribe more rationally as well as successfully those potent products derived from the glands of internal secretion, is the aim of this volume It is in no sense encyclopedic in content There are other works of greater scope for this purpose No attempt has been made to include the numerous refinements which will be of interest to those who give special attention to endocrine diagnosis and treatment Obviously, these men can be satisfied with nothing less than the monographic treatises on the individual glands and diseases concerned Owing to the rapid development of the scientific laboratory work in endocrinology, the clinician is often at a loss to know the up to-date diagnostic methods and the most dependable therapeutic preparations for his problem This will continue for years to come No one realizes more than the author how this volume will in some respects be out of date almost as soon as it has been crystallized into printed form With the hope that it may be a signpost along this path of progress, it is published in response to requests for the printing of a series of lectures given before a variety of medical organizations during the last two years

It is a pleasure to express gratitude for the cooperation in the clinic, the laboratory and with this manuscript of Dr Edgar S Gordon and Dr Marian S Kimble

—ELMER L SEVRINGHAUS, M D

Madison, Wis July 1 1938

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THE BIOLOGIC SIGNIFICANCE OF HORMONES

What to Expect of a Hormone

It is easy to exaggerate the clinical importance of endocrine therapy The hormones are being implicated in an amazing variety of situations by authors of current clinical reports It is at times difficult to sift the chaff from the wheat There are two tools which make the sifting process easier These are fundamental concepts of hormone action which apply to all the internal secretory products from specialized glands They may be summed up in two words *catalysis* and *correlation* Application of these two concepts will help the clinician to steer a sane middle course between the extremes of enthusiastic exaggerated claims and pessimistic refusal to apply laboratory findings of definite significance in the clinic

Catalysis is a chemical concept referring to the manner in which a very small amount of an active substance can cause a tremendous speeding up of a reaction No new process is introduced but the 'molecular machinery is caused to operate so much more rapidly that the reaction is completed in a fraction of the time required without the presence of the catalyst One of the simplest examples is that of thyroid action The animal body devoid of thyroid

secretion consumes oxygen and liberates energy at a low rate, but compatible with life The usual amount of thyroid secretion provides sufficient thyroxine to catalyze this use of oxygen and liberation of energy to a level about 65 per cent higher than in the thyroidless state The latter level is what we call "normal basal metabolism' If the thyroid gland is overactive, the supply of catalyst may accelerate the oxidation process by as much as 200 per cent above the thyroidless level If the thyroid fails to provide enough secretion (i e catalyst), the basal metabolism will be measurably low With complete failure, the metabolism is about 40 per cent below that of the healthy normal This concept of catalytic activity applies to all hormones, although there are no other physiologic processes which can be measured so easily and expressed in such simple mathematical terms as in the case of the thyroid This way of thinking about hormones is of increasing importance It helps in differential diagnosis in distinguishing degrees of severity of disease and in rational plans for grading hormone doses

Correlation is usually thought of as the function of the nervous system The communication of impulses by chemicals circulating in the blood and lymph is slower and more primitive, but also more general, in the whole field of biology The simplest example is the control of respiratory exchange by carbon dioxide and oxygen concentrations This is not included in the group of hormone processes because the correlation is incidental to the use of oxygen and

elimination of carbon dioxide Very different is the situation with the hormones of the ovary Their prime function is in controlling the extent of the development of the muscle and lining of the uterus, the secretory activity of the vaginal mucosa and the mating and maternal instincts of the woman so that successful impregnation may follow the liberation of the matured ovum Here is a most elaborate chain of sequential actions, where the hormones provide the mechanism for effecting correlation of the various parts of the reproductive organs with an essential nicety of balance in time and quantity The concept of correlated activities, involving tissues remote from each other, applies also to all the endocrine organs *Obviously the correlating forces* will be applied to all tissues because of hormone distribution through the blood Those tissues will respond most markedly which have the appropriate capacities So for example, the clinician must bear in mind the possible effects of thyroid on the heart, brain, bones and liver when he considers using thyroid therapy to speed up weight loss in a case of simple obesity The correlating capacities of hormones if kept in mind will help to prevent abuse of endocrine therapy

POLYGLANDULAR SYNDROMES

There is a further sense in which the endocrine glands enter into bodily correlations It is recognized that frequently syndromes which involve quantitative disturbances of activity of one gland show evidence of lesser *degrees of malfunction in one or*

more of the remaining glands Several such mixed pictures or polyglandular syndromes have been de scribed, often with the names of the original observ ers attached, which tends to perpetuate their con cepts Extensive experience in such observations makes it certain that there may be overactivity of any one gland with normal, subnormal or supernormal function of almost any other of the group of glands On mathematical grounds, the number of different syndromes that can be expected in this way becomes prodigious, especially when one remem bers that after involvement of the second gland in such a process, a third gland is possibly still more disturbed Any attempt to give diagnostic names to such mixed pictures is misdirected effort. With the constantly increasing ability to make diagnoses in terms of anatomic physiologic and chemical disturbances, diagnostic terms would be better limited to statements of over- or underactivity of each gland thought involved in a given case It may be possible at times to indicate which is a primary disturbance and which secondary

The problem becomes difficult because of the peculiar position of the pituitary secretions in the correlation scheme The pituitary produces a material which stimulates the growth and activity of the adrenal cortex, and the cortex atrophies markedly but not completely if the pituitary is destroyed Therefore the adrenal is known to depend on pituitary secretion for its own ability to produce the cortical hormone at the normal rate One may therefore have cases of adrenal

cortex deficiency which are primary, i. e., due to adrenal failure, or secondary, i. e., due to failing adrenotrophic action on the part of the anterior pituitary. But since the adrenal cortex is itself essential for life, it is true that without the adrenal the pituitary will ultimately fail. Is there also a specific secretion of the adrenal to stimulate the pituitary? Without going into the evidence, it may be said merely that the effect of the adrenal on the pituitary is only one aspect of its effect on all active parts of the body. In other words, we now believe that the pituitary produces a highly specialized secretion which is directed toward the adrenal cortex, but that the adrenal cortex produces a secretion which is specialized in terms not of an end-organ but of biologic processes without which life cannot long be maintained.

It is especially true of the anterior pituitary gland that it produces effects in other individual glands by means of the hormones which are still recognized entirely by these effects, none of them being available so far in a state pure enough to allow chemical identification. Most of the anterior lobe functions may be classified in this way. The greatest difficulty in such a classification would be with the growth factor, which has recently been spoken of as the "chondrotrophic" hormone, for its effects are most vividly demonstrated in the growing cartilages. The growth-promoting extracts increase nitrogen metabolism of anabolic type and produce increased amounts of a number of connective tissues including bone and cartilage. Although the normal type of growth de

pends on secretion of thyroid, parathyroid, adrenal, pancreas and gonad hormones, there is a marked growth-promoting effect of anterior pituitary extracts without the presence of all these The growth promoting material may be identical with the substance which stimulates secretion by the well developed mammaries

NEURO-ENDOCRINE CORRELATIONS

There are further correlations involving the endocrine system In a few cases nerves are known to carry stimuli to the glands and to affect secretory rates The innervation of all the endocrine glands is poorly known The reverse process—the modification of nervous system activity by the level of endocrine secretion—is well known but hard to measure as in the mental and reflex effects of thyroid disease, diabetes mellitus tetany and the climacteric This correlation between the two correlating systems nervous and humoral, must be further explored

Insist on Prescribing Standardized Products

It is now evident that diagnosis of endocrine disorders is becoming gradually more and more quantitative that is, we discriminate differences in *degree* of activity of a gland Therefore therapy must be similarly quantitative as we apply measured doses of active hormone preparations In only a few cases can we use chemically pure or synthetic substances as thyroxine, epinephrine, estradiol estrone proges

terone and testosterone But for every gland preparation which is clinically worth while, we can use extracts with potency determined in advance by chemical tests or biologic assays The development of these assays has relieved the clinician entirely of the cloud of doubt that existed when he could use only preparations which he hoped contained the active hormone Since we can now have an extract with tested potency for every gland action which is demonstrable in the human, there is no need to prescribe any hormone other than one of known chemical purity or in a standardized extract of labeled potency The savings of time, money and results which adherence to this policy can help us achieve are well worth the effort

CHAPTER 2

SYSTEMATIC ENDOCRINOLOGY

Simplification of endocrine relationships would be quickly accomplished if it were possible to list one or only a few functions for the secretion of each gland Some clinicians have long maintained that the activities of the various endocrine glands are so interrelated that disturbance of one gland leads to altered activity of all others The results of the careful laboratory work on animals in the past two decades tend to give support to this clinical impression This need not lead to hopeless confusion, nor should it become an excuse for reviving the use of mixed gland preparations in the clinic It is now clear that if an animal is made diabetic by pancreatectomy, the diabetes is made somewhat less severe by thyroidectomy and it becomes very mild following either adrenalectomy or hypophysectomy In other words, deficiency of the pancreatic hormone makes the normal activity of thyroid, adrenal or pituitary relatively in excess of the animal s tolerance so far as sugar metabolism is concerned It would be foolish to treat a diabetic with a mixture of hormones from these four glands although all four are disturbed There is a deficit of one and a relative excess of the other three, or, to change the comparison, if the ovaries are removed or come to the spontaneous atrophy of the climacteric

there is a morphologic change in the anterior pituitary, which secretes an increased amount of the hormone which stimulates the ovaries It would be illogical and clinically useless, to treat a woman at this time with a mixture of ovarian and pituitary hormones, for she has already an excess of one and a deficit of the other

The emergence of such information has given rise to the concept of a dynamically balanced group of glands Since it is evident that disturbed activity of any one gland may lead to some altered rate of activity of one or more of the other glands, the group must be studied together But for definiteness we may approach a systematic study by concentrating our attention on the principal and direct effects of each hormone or active extract The interglandular relationships will then become not only more evident but also easier to understand In clinical diagnosis and therapy this will lead to attempts to find the endocrine process which is primarily at fault, to think in quantitative terms and to prescribe standardized extracts of one gland at a time Although such logic may sometimes lead a conservative clinician to withhold endocrine therapy this course is preferable to prescribing treatment which might possibly harm the patient

OUTLINE OF SYSTEMATIC ENDOCRINOLOGY

It is urged that the following summary of the present state of knowledge about systematic endocrinology be read before any attempt is made to

concentrate on advances in the work on one gland

A The Pituitary Group

I Posterior Lobe This tissue produces a pressor and an oxytocic material The pressor factor is produced in response to stimulation from nerves that come through the stalk of the pituitary from nuclei in the hypothalamic region Destruction of these nuclei, interruption of the tract or destruction of the posterior lobe will therefore lead to deficiency of this pressor secretion The action of this combined neurohumoral reflex may be sketched as follows Loss of water by any route leads to increased concentration of blood plasma electrolytes, especially salt This stimulates the center in the hypothalamus, from which impulses pass over nerves to the posterior pituitary, which secretes the hormone The latter passes via the blood stream to the kidneys where it stimulates increased reabsorption of water from the tubules thereby reducing the rate of water loss until water intake replenishes the deficit and stops the reflex activity The secretion of oxytocic material has less (or no) nervous control

(a) Vasopressor material (Pitressin, Parke Davis and Company) is a short-acting stimulant to involuntary muscle in the vascular system and intestine It also

has the effect of stimulating the reabsorption of water from the renal tubules

(*b*) Oxytocic material (Pitocin, Parke, Davis and Company) is recognized by its stimulating action on myometrial contraction

II Intermediate Lobe Some extracts from this part of the pituitary gland have shown marked ability to cause changes in the melanophores of amphibian animals Other extracts influence the erythrophores in the skin of certain fish None of these intermediate lobe materials has been shown to be physiologically important in man nor have therapeutic results been *studied sufficiently to allow any recommenda* tions to be made regarding their clinical use

III Anterior Lobe The results of hypophysectomy are thought to be due essentially to ablation of the anterior lobe Widespread effects are well substantiated and include effects on the glands listed below The transplantation into hypophysectomized animals of anterior lobes or whole pituitaries, or the injection of suitable extracts, has been found to restore these glands more or less successfully toward a normal status A large variety of different extracts has been tried and there has been some tendency to

speak of as many as 12 different pituitary hormones None of these is known in a pure state, and therefore judgment as to the number of separate substances produced by the anterior lobe must be reserved The separation in some cases is not as certain or quantitative as in the posterior lobe extracts Any report of work with such extracts should be specific in stating the source of material and the method of preparation

(*a*) Thyrotrophic Effects The thyroid is *caused to undergo hypertrophy and hyperplasia* by certain anterior lobe extracts Hypophysectomy is followed by thyroid atrophy This leads to speculation about primary vs secondary thyroid disturbances and to the division of the latter into subtypes due to endocrine or nervous causes The functional importance of the thyroid innervation is probably limited to vasomotor effects

The characteristically brief period of stimulation which can be produced in an animal's thyroid as judged by histologic examination, or in human thyroid activity as judged by clinical methods, following the injection of these thyrotrophic extracts makes it difficult to explain the supposed normal dependence of the thyroid on pituitary stimulation

Thyroidectomy and thyroid feeding are both known to cause cytologic changes in the anterior lobe, demonstrating reciprocal effects between the hypophysis and the thyroid

The thyroid appears to secrete just enough of its hormone to maintain the normal rate of metabolism for the entire body It is unknown whether the gland responds to this basal metabolic rate, to oxygen concentrations or to the circulating concentration of the hormone If and when the mechanism for this control is determined, it will become possible to plan far more rational therapy for thyroid disorders

Thyroxine, the most active agent yet isolated from the thyroid, is known in pure form The nature of the molecular structure of the hormone in vivo is still being studied It is possible that when thyroxine is part of a larger molecule it is still more active Iodine is essential to the formation of thyroxine and is, therefore, a necessary element in nutrition for persons of all ages It is recognized that although iodine deficiency is the commonest cause of colloid goiter, there are probably other factors in some cases It may be that certain infections, dietary disturbances or excessive growth rates increase

the need for iodine For details on thyroid chemistry and physiology, see Harington's monograph, *The Thyroid Gland*[1]

(*b*) Parathyroid Glands Rather meager evidence indicates that the pituitary contributes a factor which stimulates the activity of these glands These structures are important in the mechanism for regulation of the circulating amounts of phosphorus and calcium, the excretion of these elements and their deposition in or mobilization from certain tissues The hormone shares this responsibility with vitamin D

The vitamin responsibility involves several features of mineral metabolism, such as facilitating calcium absorption from the gut, and effects on the organic substances in bones, teeth, etc, which make possible the deposits of calcium and phosphorus Vitamin effects on other aspects of phosphorus metabolism are suspected The exact mechanism of parathyroid hormone activity is also known in fragmentary fashion According to the simplest theory, proposed by Albright, the parathyroid hormone seems primarily concerned with adequate excretion of phosphorus Retention of phosphorus tends to depress serum calcium Exces

1 Cha 1 Robert Harington, The Thyroid Gland (London Oxford University Press, 1933)

sive excretion of phosphorus tends to lower serum phosphorus content and secondarily, mobilization of calcium with increased serum calcium content. Low serum calcium or high serum phosphorus concentrations appear to be stimulants to increased secretion of hormone by the parathyroids. High calcium or low phosphorus tends to depress the gland function. Thus the hormone represents a part of a homeostatic mechanism for maintaining a steady state for these two minerals.

Deficiency of parathyroid hormone is followed by the clinical picture of tetany. Since the discovery of this hormone a clinical syndrome of hyperparathyroidism has been recognized and described with several variations. The responsibility of hyperparathyroidism for decalcification of bones, metastatic calcifications and renal lithiasis is important.

The hormone is not yet available in a pure form. Using the crude extracts available commercially, clinical management of tetany is still difficult because the effectiveness of the injections decreases with long continued use. No explanation for this phenomenon is available.

(*c*) Mammary Glands. The pituitary influence on these glands is both direct and

via the ovaries Estrogen and progesterone are factors necessary to cause mammary growth, following which the lactation hormone initiates lactation The maintenance of secretion is dependent on nervous reflexes from suckling Relations with the corpus luteum include the main tenance of a corpus luteum during lacta tion, the mechanism not being known The lactating mammary glands in the human commonly inhibit the sex cycles in the ovaries The lactation hormone is distinct from sex stimulating extracts of the pituitary There is no satisfactory evidence that the mammary glands pro duce anything with endocrine activity elsewhere in the body

(*d*) Pancreas The islands of Langerhans seem to be stimulated to growth and activity by extracts of the anterior lobe The results of the laboratory work of the past 10 years in this field cannot yet be stated in clinical terms They certainly indicate more than one way in which the anterior *pituitary affects carbohydrate metabolism* Stimulation of the pancreas to greater insulin production appears increasingly probable Excessive action of this type may lead to exhaustion of the island tis sue, with production of diabetes mellitus

The pituitary also stimulates the adrenal cortex, which in turn is responsible for converting protein to glucose and for maintenance of glycogen stores in the liver It is significant that experimental diabetes following pancreatectomy in animals may be alleviated by hypophysectomy or by adrenalectomy There are further relations between certain pituitary extracts and changes in blood fats, increased ketosis, altered fat storage in liver and altered glycogen storage in muscles It is too early to bring these varied effects into a harmonious picture In most diabetic patients there are no obvious reasons to suspect pituitary disorders There is, however, increasing reason to suspect disturbed carbohydrate metabolism in many patients with other alterations of pituitary functions

Insulin remains the important secretion which it was found to be in 1922 Constitution of the molecule is still unknown The function of the hormone seems to be that of facilitating the metabolism of dextrose i e significantly increasing the rate of certain reactions which may go on at a slow pace in its absence

Experimental study of diabetes mellitus led to the discovery of insulin, and the insulin reaction or shock led to recognition

of a new clinical syndrome, which is called hyperinsulinism This is not infrequent, it may be clinically important or may occur as only a mild exaggeration of the normal hunger phenomena The usual stimulant for insulin secretion by the pancreas is an increase in sugar concentration in the blood reaching the pancreas The duration of insulin action is several hours and its intensity declines slowly The result of insulin action is the utilization of the blood sugar, with a reduction of the concentration of circulating sugar to its previous level If insulin action persists and sugar absorption from the gut is brief or only small in amount use of sugar from the blood may well proceed to a point when circulating sugar is at a far lower concentration than is optimal for the tissues The responses of the central nervous system to this hypoglycemia constitute the 'insulin shock' It may be produced therapeutically or spontaneously by disproportion between insulin production and sugar absorption rates Such disproportion is the mechanism for exaggerated hunger occurring one to three hours after meals, especially in children Erratic occurrence of this reaction is characteristic of pancreatic tumors

Fat metabolism is involved in diabetes

mellitus, as shown by immediate ketosis when severe diabetes is inadequately treated, and emaciation (loss of fats) and fatty deposition in the liver when the diabetes is neglected over long periods Tradition ally this has been explained as secondary to the inability of the tissues to use enough glucose, following which fats were mobilized in unusual amounts, but could not be oxidized completely More recently it has been demonstrated that dietary choline, normally secured in lecithin, is essential for liver metabolism of fats Furthermore, pancreatic extracts, free from in sulin, have been shown to prevent the ex cessively fatty livers of pancreatectomized dogs treated with insulin This may indi cate a second pancreatic hormone, to which Dragstedt has given the name 'lipocaic ' We have no knowledge about its significance in human diabetes

(*e*) Adrenal Glands Only the cortex of the adrenal is known to be dependent on the pituitary for its integrity but this connection is certain Conversely, adrenalectomy leads to marked changes in the anterior lobe as it does in many other tissues It is found that removal of either pituitary or adrenal cortex leads to atrophy of the gonads this is repaired by the

use of pituitary injection in the absence of the adrenals but not by adrenal cortex injection in the absence of the pituitary The effect of the pituitary is direct, that of the adrenal only indirect and due to the adrenal effect on the pituitary Such mixed effects are responsible for varying pictures in clinical Addison's disease and for the partial clinical control sometimes attained by the use of the current extracts of the adrenal cortex after long continued adrenal deficiency has led to extensive dis turbance of function in other organs

The cortex is now known to be con cerned with the maintenance of optimal concentrations of sodium and potassium in the blood and maintenance of normal blood volume, with muscular endurance, with resistance to infections and with formation of dextrose from protein It seems probable that the "diabetogenic" and "ketogenic" hormone effects reported in animal experiments are mediated at least in large part through the adrenal cortex

Attempts to identify the cortical hormone have led to reports about a number of crystalline compounds with various composition but all related to the same phenanthrene cyclic nucleus which is fundamental to the hormones produced by

the gonads Which is the actual hormone of the adrenal cortex, or whether there are two or more hormone molecules concerned, are questions still undecided Under abnormal conditions there may be some slightly distorted forms of this molecular structure secreted, which result in clinically recognizable conditions This is one theoretical explanation for the varied forms of hirsutism, virilism, etc , in females and for the whole group of disturbances thought of under the term of Cushing's pituitary basophilism Such patients may have pituitary tumors, or atypical pituitary cells with no tumor, but frequently tumors or other pathologic conditions are found in the adrenal Sometimes the ovary, testis or thymus is the site of tissue abnormalities Similarity in embryonic origin and chemical products of adrenal cortex and gonad seems to offer a point of approach in understanding this problem It is not probable that excess of normal adrenal cortex hormone is the etiologic factor in these clinical anomalies

About the physiologic factors which control varying secretory activity by the adrenal cortex we know almost nothing Pathologic evidence makes it certain that the gland responds with increased activity

to varied toxemias Animal experiments indicate that the administration of large doses of potent cortical extracts is followed by decreased pituitary stimulation of the adrenal cortex and atrophy of the adrenal Clinical experience indicates that the use of minimal adequate doses of extract in Addison's disease may be followed by increased adrenal cortex function

The contiguity of the adrenal cortex and medulla suggests an inquiry as to whether they are functionally connected At present we can do little more than speculate and plan experiments to verify this

The adrenal medulla is intimately associated with the involuntary nervous system and produces its hormone, epinephrine on nervous stimulation Epinephrine is a well known chemical compound Its secretion is a part of the emergency mechanism and emotional response of the body and has important effects in increasing oxygen metabolism, increasing glycolysis, decreasing dextrose combustion in muscles, besides its effects on the physical processes of circulation and respiration digestive tract activity etc

(*f*) The Gonads The anterior lobe is indispensable for the full development and

maintained activity of the ovaries or testes It is fairly certain that there are at least two separable pituitary gonadotrophic substances, i e, hormones affecting the gonads They are termed follicle stimulating and luteinizing hormones, be cause their identities are best known in work with female animals Gonadectomy also leads to pituitary changes demon strating reciprocal effects as for the thyroid and adrenals

1 The Ovaries Under the influence of the follicle stimulator the follicles mature At a certain stage of maturity the follicle ruptures the ovum is extruded and the corpus luteum is formed and goes through its period of atrophy, to be followed by another similar cycle The ovarian cycle depends on the proper sequence of action of the pituitary hormones The changes in the active amounts of these hormones and the control exerted on pituitary action by ovarian hormones are the mechanisms now being investigated in the search for the mechanism providing the control of menstruation

The graafian follicle produces and contains estrin or estrogenic hormone

This material is responsible for the development of the mammary glands, the myometrium and the endometrium, the maintenance of the adult type of vaginal mucosa and for the female secondary sex characters

The corpus luteum produces and contains more than one hormone The best known, called progesterone, causes a change in the endometrium which developed under stimulation by estrogen This change is spoken of as the progestational or premenstrual change Progesterone tends to oppose the effects of estrogen in certain ways, including a reduction in myometrial contractions There is in some species a corpus luteum material, distinct from progesterone, which leads to relaxation of ligaments in the pelvis of the gravid female The existence of this 'relaxin" has been detected in human blood early in pregnancy

The most important chemical compound of the estrogen group is estradiol (dihydrotheelin) which appears to be the chief or possibly the only form in which estrogenic hormone is manufactured in the ovarian follicle Estrone (theelin) has been found in the ovary, and it may be physiological-

ly important, although its potency is far less Both these materials are inactivated by liver and possibly other tissues A small fraction of any estradiol or estrone administered may be recovered from the urine, where it occurs as a mixture of estradiol, estrone and estriol (theelol) Some of this excreted material is free, and the rest is conjugated with glycuronic and sulfuric acids Since excreted estrogenic materials represent such a small and variable proportion of that acting in the body, urinary estrogen assays are of limited value in physiologic or clinical studies Progesterone is excreted in large amounts as a slightly altered form called pregnandiol, conjugated with glycuronic acid This material can be isolated and then weighed in terms of a few milligrams per 24 hours, when the corpus luteum is functioning well It is uncertain what proportion of progesterone appears in this form

Exact chemical constitution is known so that synthetic production has been accomplished with estradiol estrone, estriol and progesterone The synthetic materials are identical in biologic activity with the naturally oc-

curring hormones In some cases the
synthetic substances are now in com
mercial use For a number of reason
there has continued to be a desire t
measure the amounts of all these sub
stances in terms of some biologic uni
rather than to use weight units suc
as milligrams The League of Nation
has established international units I
the case of progesterone 1 unit is 1 mg
For the estrogenic materials the prob
lem is complicated by the varying type
of activity exhibited by the differen
molecules, so that the comparisons be
tween different pure substances an
mixtures vary, depending on whethe
one uses the vaginal opening in imma
ture animals, vaginal estrus change
in castrates uterine changes in cas
trates or some variation of these as th
end-point in the test The definitio
is that 1 unit is 0 0001 mg of a larg
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by direct comparison in the same lab
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animals A similar unit is specifie
for benzoate esters Mixtures of estro
gens or new materials must be com
pared with these standards Thi

method does not give comparative results in the same ratio as the clinical effectiveness of the several types of estrogen At present there is no simple solution for this puzzling situation

The reciprocal effects of ovarian hormones on the anterior pituitary are still confusing Sustained use of large doses of estrogenic materials in experimental animals leads to depressed production of gonadotrophic hormones Short time experiments and use of smaller doses do not give the same results At times there appear evidences of stimulation of pituitary function following estrogenic therapy in animals The matter requires more quantitative study These varied effects may well be correlated with the disconcerting variety of anomalies in human menstrual cycles and the disagreement about results from experimental therapy with new endocrine preparations in the past decade

Menstruation is a phenomenon still without generally accepted definition A bloody flow from the endometrium can be obtained by the action of adequate doses of estrogen followed by marked reduction or withdrawal of the

curring hormones In some cases these synthetic substances are now in commercial use For a number of reasons there has continued to be a desire to measure the amounts of all these substances in terms of some biologic unit, rather than to use weight units such as milligrams The League of Nations has established international units In the case of progesterone 1 unit is 1 mg For the estrogenic materials the problem is complicated by the varying types of activity exhibited by the different molecules, so that the comparisons between different pure substances and mixtures vary, depending on whether one uses the vaginal opening in immature animals, vaginal estrus changes in castrates uterine changes in castrates or some variation of these as the end-point in the test The definition is that 1 unit is 0 0001 mg of a large sample of purified estrone which has been deposited at London The unknown and the known must be tested by direct comparison in the same laboratory and on the same group of animals A similar unit is specified for benzoate esters Mixtures of estrogens or new materials must be compared with these standards This

licles in the ovaries

The menopause, with varied clinical picture, has been found to be produced essentially by the withdrawal of estrogen from the body The corpus luteum is of slight importance in this matter Replacement therapy with commercial estrogenic preparations is comparable in its symptomatic success to the use of thyroid in myxedema The hormone can be given orally although larger doses are required than when it is injected parenterally This is probably due to the rapid inactivation of estro gens by the liver

2 The Placenta During pregnancy, the products of conception, probably the placenta, produce materials of importance in several ways In addition to increased amounts of estrogenic substances there is produced a large supply of substance that is in many ways like the anterior pituitary gonad stimulating hormones It is certain that this is chemically distinct from the anterior lobe hormone, in fact the placenta produces something which inhibits the pituitary during pregnancy This anterior pituitary like (A P L) substance may contribute to maintaining the cor

hormone The flow can be inhibited for long periods if the estrogen dose is maintained or also if it is followed by a maintained dose of *progesterone* Progesterone leads to a premenstrual endometrium, but flow does not follow *until* progesterone is omitted *or the* dose greatly reduced In humans as well as in animals, both the follicular and the lutein types of flow have been demonstrated Regularity of the periods between flows is not a dependable guarantee that the normal premenstrual changes have occurred, nor irregularity that they are absent The factors which control the circulation in the uterus are undoubtedly involved in *determining the timing,* duration and amount of flow, the amount of blood which is included in the secretion from *the endometrium (menstrual flow)* and the loss of tissue Estrogens have marked vasomotor effects, as well as action on the myometrium *thereby* representing the major endocrine factor More exact description of the process is not yet possible

The cycle of menstruation is, therefore, dependent on pituitary and ovarian hormone production and on the speed of the typical life cycle of fol-

licles in the ovaries

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pus luteum of pregnancy and to inhibiting ovulation, and it has effects on the fetal gonads The excretion of A P L in the urine is the basis of the widely used Aschheim-Zondek, Friedman and most other animal tests for early diagnosis of pregnancy This A. P L has been widely used as a clinical stimulant of the gonads in both sexes The logic of this procedure is gravely in doubt and it now appears wiser to use only genuine anterior lobe products A P L does not stimulate the human follicles but may cause some destructive changes and atretic follicles, however it may be useful in certain morbid conditions such as threatened or repeated abortion The use of A P L materials in males to produce descent of cryptorchid testes is based on animal work confirmed by clinical results It is apparent that this testicular effect is limited to stimulation of the interstitial tissue Any effects on spermatogenic tissue depend on the interstitial tissue secretion of testosterone which has some beneficial effect on spermatogenic tissue but cannot substitute entirely for the anterior pituitary gonadotrophic hormone

The term prolan' should be re

served for A P L and not be applied to anterior pituitary extracts

3 The Testes Anterior lobe stimulation is necessary for the development of the spermatogenic and interstitial tissues There are probably two or more hormones produced by the testis since the one best known does not give complete results in replacement therapy after gonadectomy in either animals or the clinic This better known material is testosterone and is produced by interstitial tissue It is excreted in a form known as androsterone The effects of administered testosterone and androsterone differ in quality and intensity Human therapy can now be based on testosterone but whether this can be used orally has not been determined Oral administration is comparatively ineffective, to say the least This testicular material is demonstrable by several effects best known among which is its stimulation of the comb growth in the capon It also causes development in the human of the seminal vesicles, of the prostate of other accessory genital structures and of some of the male secondary sex characters

The secretion of the spermatogenic tissue is in some senses still hypothetic

Physiologic and pathologic work with these male hormones is sufficiently advanced to show that there are clinical changes in the amounts circulating and excreted in such conditions as castration, some cases of premature failure of sex activity and certain testicular tumor cases There is no doubt that testosterone exerts an inhibitory effect on the pituitary production of gonadotrophic hormones Such action is part of a dynamic balance between pituitary and testicular function in the normal male This type of testosterone activity has led to its trial in reducing pituitary activity in women The method is still in the experimental stages

(g) Incompletely Defined Pituitary Functions These include suggestions of effects on (1) carbohydrate and (2) fat metabolism other than via the pancreas or adrenals or thyroid, direct effects on (1) the specific dynamic action of foods and (2) the well known growth promotion factor of the anterior lobe Although highly potent growth-promoting extracts have been produced, no product of crystalline purity has been reported It seems increasingly

probable that there is a growth hormone, which stimulates anabolic processes in protein metabolism, especially in con nective tissues The marked effects seen in growing cartilages have led to the designation of 'chondrotrophic hormone' It must not be forgotten that many other hormones, some of the vitamins and protein and calorie supply, are among factors which affect growth rates The varying pictures of gigantism, acromegaly and dwarfism as well as of the different types of infantilism may occur as consequences of varying disturbances in this one gland with slight relative changes in one or more of the factors enumerated

Miscellaneous Group of Glands

I The Pineal This structure has not been as signed a recognized function Its calcification is commonly demonstrable by x-ray in early adult life Occasional suggestions are made of pineal disturbance associated with precocious sex development

II The thymus has recently had attention from several investigators It is probably not to be considered the cause of sudden death as fre quently as formerly thought but it may cause mechanical difficulties The metabolic signifi cance of the thymus is very uncertain Since

thymic atrophy parallels adolescent development and since much animal work suggests that thymic extracts stimulate growth and especially rapid development, whereas other reports show that gonad hormone treatment of animals causes thymic atrophy, one must recognize some association between thymus and endocrine activity But the direct physiologic responsibility of the thymus is unknown The clinician must still deal with this structure on anatomic grounds There is no sound basis for thymic preparations in therapy One need not fear that radiation for enlarged thymus in infancy will distort the development or retard growth of the child Clinical observations strongly suggest that thymic tumors, possibly thymic hyperfunction, are related to myasthenia The physiologic basis of such a relation is not clear

III *Hormones of importance in the digestive processes* include secretin, which is produced by the action of acid in the duodenum and which stimulates secretion of gastric and pancreatic juices, and cholecystokinin an upper intestinal mucosal product which is a factor in gallbladder evacuation More recently there has been described an intestinal extract, enterogastrone which inhibits gastric activity None of these three has been brought into clinical use for diagnosis or therapy

IV The passage of a nervous impulse over a motor nerve leads to the liberation of small amounts of compounds which stimulate the end organs In the sympathetic system this material is sympathin (Cannon), resembling epinephrine rather closely In the voluntary nervous system it is acetylcholine, a compound of known com position The possibility of preparing related compounds with slow and sustained effects is enticing

C **Antihormones**

During the past few years much has been said about biologic reactions in animals which have been treated with certain of the relatively crude pituitary extracts Continued or repeated use of these materials in the same animal is often followed by a primary positive stimulation and later by a failure to continue the success In some cases there have been evidences of formation of im mune bodies which could be passively transferred to other animals In other cases the results have indicated a refractory state, which would allow of repeated or continued effects only after a rest period free from therapy The explanation of these phenomena in terms of antihormones has been promptly offered and is leading to much speculation about the therapy of such conditions as thyrotoxicosis It should be pointed out that there are no known cases of an antibody for any of the purified hormones thyroxine estrogenic

substances, progesterone or testosterone. Other factors which probably enter into the explanation of these refractory states include the reciprocal relationships between various glands, the exhaustion state from excessive stimulation which can be demonstrated in such cases as thyroid, adrenal, ovaries and possibly the pancreas, and the obvious cyclic activity seen in ovaries. Evidence increasingly indicates that antihormones are species-specific antibodies in the sense of classic immunity. Other factors in producing refractory states still require consideration. Antihormones are not yet useful in the clinic.

REFERENCES FOR FURTHER READING

For detailed studies of the individual glands, consult A. T. Cameron's *Recent Advances in Endocrinology* (4th ed., Philadelphia: P. Blakiston's Son & Co., 1940). This volume is well documented and presents an excellent survey of chemical, physiologic and clinical knowledge.

For details and documented studies of the reproductive group of hormones see *Sex and Internal Secretion*, edited by Edgar Allen, Charles H. Danforth and Edward A. Doisy (2d ed. Baltimore: Williams & Wilkins Co., 1939).

Chapter 3

POSTERIOR PITUITARY

Function

The posterior pituitary provides a pressor and an oxytocic material and its activity is dependent on the integrity of a nervous connection from the supraoptic nuclei through the infundibulum With destructive lesions anywhere in this tract or involving the posterior lobe, but leaving the anterior lobe intact, permanent polyuria results The physiologic significance of the pressor material is unknown aside from this action Physiologic oxytocic activity during menstrual cycles and at delivery is the subject of speculation, but the action is not demonstrated

Diagnosis

The only clinical entity definitely associated with posterior lobe disease is diabetes insipidus, a result of hypofunction Diagnosis is based on the presence of persistent polyuria with low specific gravity, 1 012 or lower, without glycosuria or evidence of chronic nephritis and with little or no reduction of the polyuria by voluntary water restriction for as long as 12 hours A search for any anatomic sources of posterior pituitary irritation or destruction is urgently indicated, because specific therapy for syphilis, irradiation for the bone lesions of the Hand-Schüller-Christian disease (xan

thomatosis) and surgical removal of intracranial tumors have been known to effect at least partial and sustained improvement

There is no accepted association of any clinical syndrome with hyperfunction of the posterior pituitary or with abnormal production of the oxytocic substance

Therapy

Helpful measures in *diabetes insipidus* are the voluntary curtailment of water intake to the point of beginning discomfort from thirst, reduction in salt intake by omission of added salt in serving food and moderation in protein intake Thyroid therapy is contraindicated for it may increase the severity of the syndrome

Specific therapy is by use of U S P posterior pituitary solution This may be given hypodermically in doses from 0 25 to 1 c c as required to control the polyuria The objective should be urine volumes of 2 to 3 L per 24 hours, thus avoiding much broken sleep from nocturia The pressor fraction is the important material but its greater expense militates against its employment except in gravid women in whom the oxytocic fraction must be avoided These extracts may be used intranasally, either as sprays with an atomizer or on cotton tampons readily placed by the patient after training The easiest and least expensive method is the use of posterior pituitary powder, used as snuff, in effective amounts and at appropriate intervals learned quickly by any patient

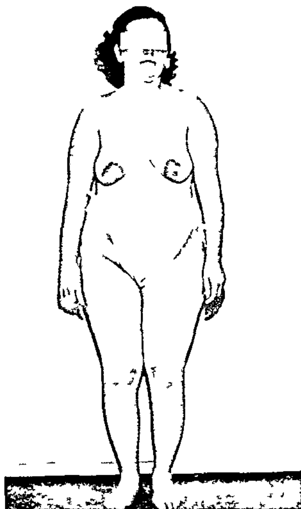


Fig 1—Obesity and diabetes insipidus This woman 23 was well until obesity began during first pregnancy *becoming progressively worse* Polyuria and *polydipsia* followed second pregnancy and menses did not return after lactation No evidence of pituitary lesion found by x ray or eye examination Diabetes insipidus was controlled by posterior pituitary therapy reducing output from 5,900 to 1,950 c.c. with fluids unlimited

The whole posterior pituitary liquid or the separate fractions in aqueous solutions or in nasal jellies are used frequently for effects which may be pharmacodynamic rather than substitutional. Thus the pressor fraction is used in cases of acute and profound hypotension and for relief from atony of the intestine after laparatomies. Its action on blood vessels or intestines is very transitory. This action is important however, for the increased blood pressure may lead to unpleasant head symptoms, or most commonly the intestinal stimulation causes a bowel cramp when an overdose is administered for relief from diabetes insipidus. Patients soon learn to keep the maintenance doses below the level which will cause such discomfort. The oxytocic substance is used widely in obstetrics to increase the postpartum contractions of the uterus. Doses of either fraction vary from 0.25 to 1 c.c.

Preparations Available

The U. S. Pharmacopeia calls for Solution of Posterior Pituitary, which is furnished in standardized ampules of two concentrations called "obstetrical" and "surgical." The former is one half as strong as the latter. Parke, Davis and Company have developed the separate fractions, vasopressin and oxytocin, which they alone market under the names "Pitressin" and "Pitocin." The term "Pituitrin" likewise applies strictly to this firm's product of the entire posterior lobe. Six other manufacturers produce the U. S. P. extract in the same potency, sold as extract or solu

tion of posterior pituitary The posterior pituitary powder is also a U S P product and is available from several manufacturers under no special name

Recent attempts to prolong the action of posterior pituitary extract have led to formation of a tannate, *which is insoluble in water or oils This is injected* in a suspension, at present available in oil The hormone is liberated slowly enough that one injected dose continues to act for 24 to 48 hours

Prognosis

Unless a specific cause for diabetes insipidus can be discovered and removed, it is a permanent disorder and will require lifelong treatment When symptomatically treated with pituitary material, the disorder does not limit life or health per se There is no contraindication to the use of minimum doses of the posterior lobe necessary for control of the symptoms

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J A Greene and L E January Diabetes Insipidus J A M A 115 1183-1185, Oct 5, 1940

J Warkany and A G Mitchell Diabetes Insipidus in Children, Critical Review of Etiology, Diagnosis, and Treatment, with Report of Four Cases Am J Dis Child 57 603 666, March, 1939

ANTERIOR PITUITARY

Since the anterior pituitary is now known to produce materials which are essential to the development and activity of the thyroid, adrenal cortex, gonads and mammary glands and possibly also parathyroids, pancreas and thymus, and since the activity of the anterior lobe is essential to growth, normal carbohydrate and fat metabolism and blood regeneration, it has become possible to group the functions of the different glands under a tentative orderly arrangement with the pituitary as the center of the scheme The order of listing of glands is anatomic from top to bottom, preceded by the general growth problem

In view of the fact that the pituitary has such varied potencies occasions are rare when a complete pituitary extract is required in clinical therapy Extracts should be prepared for specific purposes and standardized by their abilities to achieve such results in experimental animals The time when tablets of pituitary gland substance could be prescribed with clinical confidence has passed Until some method has been found to prevent destruction of pituitary hormones in the digestive tract dependable endocrine therapy with pituitary materials will have to be based on hypodermic administration of carefully standardized doses Fortunately, there are extracts from some glands such as thyroid adrenal cortex and ovaries which can be used orally with benefit The following pages discuss this increasingly important quantitative aspect of the diagnostic and therapeutic problems of the anterior lobe and related glands

Chapter 4

GROWTH FACTOR

Function

There seems to be one specific extract from the anterior pituitary which accelerates growth, however, the results of human therapy have been better when the extracts are not fractionated too highly There fore, the impression has existed that catalysis of growth by the pituitary is the summation of several stimulating actions, probably including most of the other known functions of this gland The expression of the growth stimulus is most easily demonstrated in the long bones although it applies to soft tissues as well, and can be demonstrated in such metabolic proc esses as increased nitrogen metabolism Recent re sults indicate that a highly potent growth-stimulating substance may be isolated, free from most other pitu- itary functions The striking effects of such material on growing cartilages have led to calling the growth promoter the chondrotrophic hormone

Diagnosis

Diagnosis of retardation or acceleration of growth requires the use of the conventional height-weight age tables, which must be interpreted with the knowl edge that they represent statistical "normal' individ uals, i e, that at least 10 per cent deviation from such data must be allowed before diagnosing abnormality

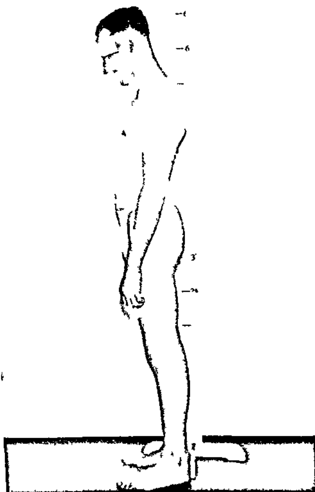


Fig 2—Gigantism Age 2? 79 in tall Growth had stopped within the twenty second year Span was 82¼ in There were petit mal attacks loss of libido and headache all of recent origin Sugar tolerance was increased No pituitary tumor could be demon trated by x ray or e e examination during the next year Use of estrogenic hor mone and later of deep x ray therapy gave temporary relief from the epileptic seizures

CHAPTER 4

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Records of growth of the individual during recent years are of greater importance than any single examination, but should be written data obtained by careful observers if the evidence is to be useful Retarded growth may be a result of undernutrition in protein, in caloric intake, in the supply of vitamins or of long continued infection When history and physical examination are competent to eliminate such causes the pituitary is implicated as the cause of *dwarfism* by common assumption The probability of pituitary responsibility is increased in those cases in which disturbance of genital development is evident, e g, the Froehlich type (with obesity also), the Lorain type dwarf (symmetrical and delicate structure, with infantile sex organs) Cretinism and achondroplasia must be eliminated as causes of dwarfism If there is doubt, x-rays of the hands and arms are helpful Marked thyroid deficiency causes delay in the development of centers of ossification Achondroplasia leads to short limbs as compared with the torso, and the characteristic x-ray pictures of the epiphyseal ends of the long bones are diagnostic

Pituitary cachexia, *Simmonds disease*, is a condition marked by profound asthenia, emaciation, decreased size of viscera, loss of sexual functions and loss of resistance to infections or severe stress It is usually terminated by death following a relatively minor illness or trauma At autopsy atrophy or destruction of large portions of the anterior pituitary are the pathognomonic findings Probably Simmonds disease results from hypopituitarism plus destruction

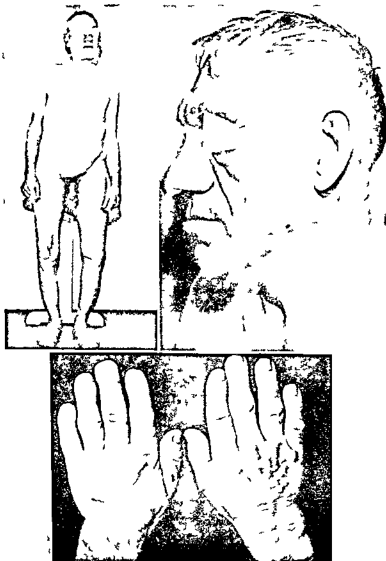


Fig 3—Acromegaly Arrested case with old tumor in sella Note prognathism and enlarged hands

of certain hypothalamic areas Antemortem diagnosis has been hampered by the close similarity of the syndrome known as anorexia nervosa, in which for various reasons extreme undernutrition occurs despite an available supply of good food and apparently normal ability to digest it Consequently, it becomes necessary to employ the most clever psychiatric approach to augment the nutritional program as the first step in therapy for such asthenic patients Beyond this point the use of pituitary extracts is still experimental The more comprehensive or "crude growth-promoting preparations may be expected to provide the more complete substitution therapy for complete pituitary failure Coincident treatment with adrenal cortex extracts is rational Reports of success in such cases are still few

Reports by Sheehan in the past few years have emphasized the occurrence of various degrees of pituitary failure following deliveries marked by a shock like picture Probably a far larger number of women have partial failure rather than complete loss of pituitary function, i e, Simmonds' cachexia It is these women who can be given some measure of relief by dietary therapy for emaciation or for the obesity which paradoxically marks some cases with hypothalamic injury The gonadotrophic materials described in Chapter 11 will be required to restore underactive gonads If response to such therapy is inadequate, substitution for ovarian secretion by estrogenic therapy may be indicated as for climacteric symptoms occurring under any circumstances

Gigantism occurs when anterior lobe overactivity is marked before the union of the epiphyses, *acromegaly* develops when the overactivity is present after the union precludes further gain in length of the long bones It is obvious that gigantism may be followed by acromegaly when the exaggerated activity con tinues After the earlier stages of the disorder, the diagnosis of acromegaly is obvious from inspection The problem in gigantism is to diagnose this process before the individual has exceeded the normal height for the adult The growth process occurs in cycles during the first two decades of life, and the last rapid growth period appears at the time when adolescent changes begin to develop Rapid growth is common at this age and often is alarming, but seldom does it lead to excessive height There is a widespread opinion that essentially normal activity of the gonads serves to accelerate the union of the epiphyses and thereby stop the growth which would otherwise lead to gigantism Epiphyseal union is known to occur despite complete absence of the gonadal secretions, and therefore, it must be recalled that the effect of these sex hormones is merely catalytic, i e, they increase the rate of such a process of bony maturity but are not necessary for the maturing process Thyroid activity also stimulates bony maturity Consequently the available methods for limiting unduly rapid growth in stature are the use of thyroid, of gonadotrophic or of gonad hormones It would be unjustifiable to attempt surgical or irradi ation therapy to reduce pituitary activity in cases of excessive growth save in the presence of a neoplasm,

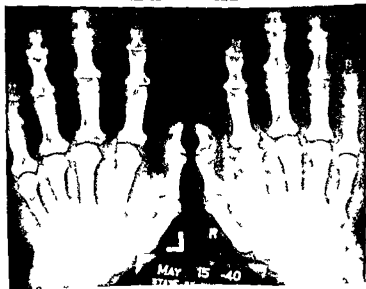


Fig 4—Same case as preceding characteristic bony changes in skull and phalanges

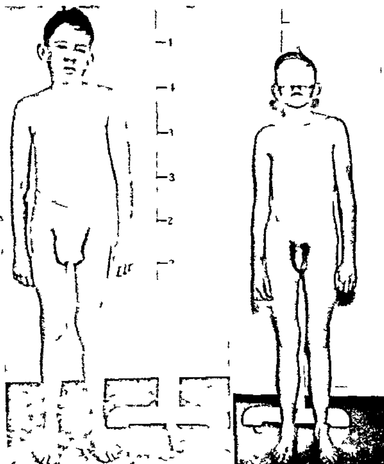


Fig 5 (left) —Dwarf 19 with diabetes partially controlled for 8 years He had not grown during last 6 years Proportion and maturity indicated Levi Lorain type No evidences of adol scent maturity Epiphyse ununited

Fig 6 (right) —Administration of growth promoting anterior pituitary extract (Polvansyn Armour) led to addition of 5½ in in 20 months with adoles ent changes of genitalia voice and attitude Diabetes became distinctly less severe and more stable

because of the possibility of permanent destruction of pituitary gonadotrophic and adrenotrophic activity

Therapy

For *dwarfism*, it is important that the diet be adequate The addition of concentrated vitamin preparations such as cod or halibut liver oils to furnish vitamins A and D and of yeast preparations or other source of the vitamin B group are worth trial Special emphasis may be given the use of thiamine (vitamin B1) if the appetite is not excellent

The dwarf whose retarded growth has not been definitely explained may be given anterior pituitary therapy even though there is no certainty of pituitary etiology This has often been done with oral preparations but the results are less certain than from the use of the newer extracts Hypodermic administration is simple the doses should be 1–2 c c daily Since the material is water-soluble and since it acts quickly and for a brief period after injection results will be far better from frequent small doses than from large doses at intervals separated by several days Increased rate of growth should appear within two to three months if the dosage is adequate but treatment should be continued until the stature has reached the optimum or until the femoral epiphyses have united (last stage of growth) It is unnecessary to interrupt such a series of injections for rest periods or to avoid antihormone formation

The preparations available for stimulating growth include at least five standardized anterior pituitary ex

tracts, sold under that name or with special trade names, as given below There is at present no information from impartial sources by which the potencies or relative merits of these extracts can be compared They are all known by both animal and human trials to be potent in stimulating growth Local reactions from the hypodermic injections are not extreme The Armour laboratory and Ayerst, McKenna and Harrison produce extracts under the name "Polyansyn and "Growth Complex" Polyansyn contains thyrotrophic and gonadotrophic materials, which are omitted from Growth Complex Parke, Davis and Company label their product 'Antuitrin Growth' The Squibb product is 'Phykentrone The Wilson laboratory calls the extract "Phyone

These same materials seem appropriate for the treatment of *Simmonds disease* The accessory use of a high caloric diet and of at least 3 mg thiamine daily to provoke appetite should precede as well as accompany the treatment Trial of insulin to provoke greater appetite must be attended with great caution because patients with Simmonds' disease are peculiarly sensitive to insulin It is important to emphasize skilful use of psychotherapy to alleviate the anorexia nervosa which has too frequently been confused with genuine Simmonds' disease (See Fig 10)

Acromegaly has been treated with irradiation or with surgery The choice will depend on regional indications (tumor optic nerve damage) Often the symptom requiring relief is headache and some patients have been relieved by nothing more than deep





Fig 7 (above) and Fig 8 (below left) —Same case as preceding Femoral epiphyses ununited before therapy
Fig 9 (below right) —Same case Femoral epiphyses united after pituitary therapy

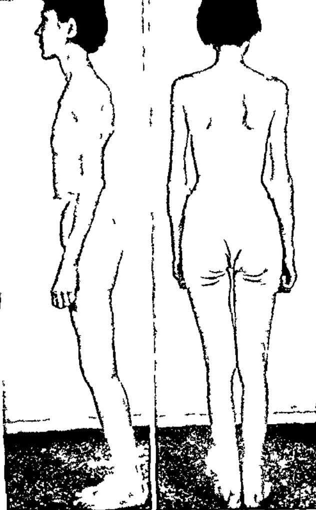


Fig 10—Anorexia nervosa simulating Simmond cachexia Age 28 Fatigue weight loss constipation poor appetite amenorrhea for seven years Pulse slow blood pressure as low as 86/52 blood sugar levels low after sugar tolerance test basal metabolism 14 29% below predictions whole blood cholesterol 222 mg per 100 cc serum protein 4 52% uterus small without endometrium obtainable by curet Responses to adrenal cortex and several anterior pituitary extracts temporary and poor Withholding of salt affected her as it does patients with severe adrenal deficiency Postmortem showed intact adrenal thyroid and pituitary glands and viscera were not small as in true Simmond disease Social factors accounted for anorexia

x ray therapy There has been some temporary success reported from the use of large doses of estrogenic hormone, which is thought to operate by exerting an inhibition on the anterior pituitary This inhibition is known to occur in small laboratory animals so far as the gonadotrophic function of the pituitary is concerned The permanence of results cannot yet be told There is no danger in this type of treatment Similar treatment in adolescent *gigantism* is conceivable, or the use of gonadotrophic pituitary extracts to hasten the completion of adolescent development might be helpful These relationships are still speculative For the present, it is best to treat acromegaly symptomatically Treatments designed to limit the growth in threatened gigantism are in the experimental stages, and dosage cannot be prescribed

Prognosis

Dwarfism must be treated before the epiphyses unite With the recent pituitary products, growth of 2 to 6 in has been achieved in the course of a few years of sustained therapy There is always uncertainty as to how much growth might have occurred without therapy

Simmonds' disease has a grave prognosis, but some cases are known to have lived for years despite this deficiency Duration of life is uncertain owing to the reduced resistance which may be a complicated form of adrenal insufficiency Results from therapy are not sufficiently definite in most cases to justify any statement about improved prognosis under treatment

Gigantism entails handicaps in disproportion of organs and the skeleton, with consequent shortening of life in addition to the social handicap of deviation from the norm Acromegaly is limited usually by the local lesion causing the pituitary disturbance and may be associated with such accessory disturbances as goiter, diabetes mellitus hypogonadism and poor resistance to infection These complicate the prognosis and make therapy more urgent, using either surgery or x rays to limit the process

processes of all cells are probably responsible for the clinical features of thyroid diseases other than neoplasms and infections Acceleration in growth and in development of the body are considered consequences of increased oxidation

Diagnosis

Excessive liberation of thyroxine into the circulation leads to *thyrotoxicosis* the name signifying the production of an intoxicated state The clinical manifestations of this state are manifold and the diagnostic pitfalls numerous The most fundamental clinical evidences of the disease are tachycardia, loss of weight combined with good food intake and excessive irritability of the autonomic nervous system Conventionally, the thyrotoxic condition is said to occur in two forms, Graves' disease and toxic adenoma The dividing line is so ill-defined that there is no general clinical agreement on diagnostic criteria for the separation The most important matter is the recognition that the toxic state may occur in patients who have an unstable autonomic and central nervous system previous to and lasting after any toxic result from thyroid overactivity (Graves' type of constitution) The demonstration of thyrotoxicosis in such patients is dependent to a great extent on reliable basal metabolism tests Precisely these patients find it hard to remain entirely calm and relaxed for the test and this failure of relaxation may produce elevated metabolic rates giving exaggerated indication of the degree of toxicity Therefore the test needs to be repeated in

Chapter 5

THYROID

Function

Anterior pituitary extracts stimulate growth and increase function of the thyroid The significance of this action in the human is still uncertain Sustained effect on hypothyroidism by thyrotrophic pituitary extracts has not yet been achieved A hyperpituitary etiology for excessive thyroid action is probable in a fraction of the cases Therefore application of the thyrotrophic principle of the pituitary must be held *sub judice* in the clinic at present

The physiologic secretion of the thyroid is probably a combination of thyroxine with a protein molecule (Fig 11) This hormone is a catalyst which accelerates the oxidation of foodstuffs and liberation of

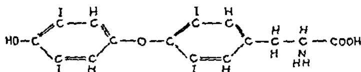


Fig 11—Thyroxine

energy The exact site of action is not known Essentially all the tissues are affected There seems to be also a specific effect on the nervous system, leading to increased irritability These two effects of the hormone in stimulating the most fundamental biologic

ter half of life, especially, should be studied as possibly thyrotoxic

Hypofunction of the thyroid is the cause of *cretinism* when it occurs congenitally, or of *myxedema* when it appears later The outspoken cases are not often missed if the retardation in mental activity, slow reflexes, somnolence, thick and dry skin, bradycardia, anemia and tendency to muscle degeneration are kept in mind as the characteristics The basal metabolism test is of dependable usefulness here unless the age or mental state prevents cooperation in the measurement of the respiratory exchange For this reason, accessory diagnostic tests are important in borderline problems The use of blood cholesterol determination is one of the better means, since elevated cholesterol content is said to occur uniformly with hypothyroidism when untreated Of course, there are other causes of hypercholesterolemia which must be eliminated in the diagnostic study The upper limit for normal whole blood cholesterol is approximately 175 mg per 100 c c The dependability of serum cholesterol determinations is superior for such diagnostic work Upper normal limits for serum cholesterol are taken as 275 mg per 100 c c But given a borderline problem the finding of normal cholesterol concentration serves to eliminate hypothyroidism more satisfactorily than a normal basal metabolism The latter might be found within normal limits because of apprehension or excitement Studies of iodine tolerance and of creatine tolerance are promising but still limited to use in clinics with large laboratories

doubtful cases until consistent results are achieved It must be carried out by an operator who understands both the technic and the psychologic problem, and the patient must be specially prepared for the test by explanation by the clinician Obviously, the use of accessory diagnostic tests is desirable Of those proposed, the only promising one at present is the study of blood iodine The technic is not yet simple enough for use away from specialized laboratories This diagnostic problem is of importance in a discussion of therapy, because it determines the decision whether to treat the nervous system with sedation, psychotherapy, etc , or to treat the thyroid with iodine, surgery or irradiation Also, there is a persistent problem of treating the nervous element in these patients after the thyroid problem has been dealt with The persistence of this nervous problem may lead to a mistaken diagnosis of recurrent thyrotoxicosis

Cases of thyrotoxicosis with adenoma usually occur in older patients, probably because this condition is the result of a series of exacerbations and remissions of minor attacks of the thyrotoxic state, with the adenomas recording the tissue response to hyperplasia and resting stages The mechanical problems of the tumor and the risks of neoplasm will not be discussed The direct results of the long continued, often undiagnosed toxic state in an individual who has endured the vicissitudes of several decades are shown especially in the heart This complication constitutes the most urgent reason for treatment Conversely, any patient with unexplained heart disease, in the lat-

parenteral glucose therapy for protection of the liver is important in the more toxic cases Further protection for the liver may be provided by ample use of the vitamin A and B groups It is probably wise to administer thiamine in oral doses of 3 to 10 mg daily until evidence of the toxic state has passed The vitamin is thought to act by facilitating dextrose oxidation and storage It does not directly reduce the toxicity of the thyroid state The optimum time for thyroidectomy is reached when the pulse has slowed, weight has been gained and the nervous system has been perceptibly stabilized At such a time, basal metabolism will also have descended to a lower level or 'plateau" If manifestations of improvement are not secured, the prognosis for successful operation and for postoperative quiet convalescence is poor

Thyroid crisis is a term applied to a sudden and severely toxic state occurring especially after thyroidectomy and marked by extreme tachycardia, fever of alarming degree, anxiety and a general exaggeration of the thyrotoxic picture This may appear within a few hours after operation It has often been attributed to sudden flooding of the body with thyroid hormone as a consequence of the mechanical disturbance of the thyroid which is thought to express the hormone into the blood stream This concept is being replaced in many quarters by a belief that the fundamental trouble is probably cardiac and hepatic damage The change in point of view is due to the decreasing frequency of these crises or storms in the hands of those organized hospital groups where careful preoperative medical

Therapy

For *thyrotoxicosis* there are three methods of demonstrated benefit medical, surgical and irradiation The medical consists of sedation, elimination of foci of infection, psychotherapy and occupational readjustment This is to be used in mild and acute cases, especially when the exciting factor is recognized It is probably the least reliable method of treatment and depends largely on the known tendency of the disease to have remissions Exacerbations are frequently seen It is largely for this latter reason that thyroidectomy has become so popular as the method of choice The tendency is to subtotal removal of the gland, with care to leave the lateral poles, since they usually contain the parathyroids Proper preparation of patients for this surgery demands first of all the use of iodine orally, which brings about a remission in the toxic state in a majority of patients within 10 to 20 days The form of iodine is not important, the amount required is small The conventional medicament is compound solution of iodine (Lugol s), but simple sodium or potassium iodides are just as good The dose of Lugol's solution needed is probably not over 1 minim daily but larger doses do no harm With the iodides, doses of 65 mg given as 1 minim of the U S P saturated solution, are equivalent to at least 5 minims of Lugol's solution Accessory factors of importance are a program which will insure rest and sleep, using sedatives if needed and elevation of the caloric intake to such a level that a gain in weight occurs before operation High carbohydrate feeding or

tein and, intake, they do not reduce the carbohy dr hen there is any gastro-intestinal dis- may interfere with feedings, per cent dextrose injections may advantage of this method is ques food can be taken orally and well

General Practice (M-45)

n supplements to the diet has come of the treatment of thyrotoxicosis s is due to the demonstration in is that thiamine has a beneficial as well as on the heart and the The normal liver has a consider- in B A second factor in the B of vitamins, riboflavin, is now nstituent of the oxidative enzyme nost of the tissues With thiamine nstrated to be indispensable fac- hydrate metabolism it is clinically he mechanism of dextrose utiliza- Ve do not yet know whether the itamin B are important in treat osis It is wise to use liberal l vegetables in the diets of all thy- ssary, to supplement limited in- es of the B group such as yeast res in preparation for thyroidec- good practice usually includes at re more than an average amount ility to relax and maintain bed arative period The barbiturates

preparation has been developed in the 23 years since H S Plummer revived the use of iodine for thyrotoxicosis It appears that the protection need not be directed so much toward the thyroid gland as toward the heart and liver of the patient menaced with crisis

Prevention of crisis depends, therefore, on thorough going application of the known helpful measures in preoperative care the wisest choice of the time for surgical intervention and the use of the two stage operation when the risk is great The use of iodine has already been dealt with The diet needs to be ample in carbohydrate not only to replenish the reduced storage of liver and muscle glycogen but also to furnish the sugar which is being consumed at an unusually rapid rate so long as the basal metabolism is above normal Liberal carbohydrate feeding is now known to be most important in the protection of a liver damaged in any one of several ways Tremendous doses of carbohydrate in any form are not helpful, since there is a limit to the rate at which sugar can be absorbed and stored The more important matter is the frequent feeding of moderate amounts with care that there shall not be intervals of many hours without some intake of sugar or starch There are recent reports that it is wise to reduce protein and fat feeding to a minimum at the same time Of these probably the protein is more important, since protein catabolism imposes extra tasks on the liver and also serves as a stimulant to total metabolism The merit of the recently proposed undernutrition regimes for

Before these factors in technic had been so well developed, it was discovered that the risk of thyroid crisis was less if only one half the thyroid was removed at one time This has been abandoned in many places, but with cases in which the toxic state is poorly controlled by the aforementioned measures, it appears that hemithyroidectomy still has a place The advantage from use of iodine will not be so great when the second operation is to be attempted, but the toxicity of the patient will also be reduced in many cases by the first operation The choice of anesthetic agent is probably not so important as the choice of anesthetist In other words, with modern anesthetic agents a skilled operator can use any one of several drugs choosing that one with which he is most certain that he can maintain an excellent supply of oxygen throughout the operation and can also keep physically out of the path of the surgeon These and other reasons lead some surgeons to prefer local anesthesia for goiter work

Postoperative care requires observation to be certain that oxygen supply is adequate If there is doubt, the use of oxygen by the intratracheal catheter is especially helpful Fluids must be furnished at short intervals because of the exaggerated rate of water loss due to the high basal rate the anesthesia, the operative shock and possibly the occurrence of fever Intake of dextrose needs also to be provided for without delay This should be given parenterally as 5 per cent solution, in amounts of 500 to 1,000 c c at least three times daily until oral food intake is dependable If

are usually the sedatives of choice, given in doses of 30 to 60 mg (½ to 1 gr) t i d , phenobarbital perhaps to be preferred because of its prolonged action and its emphasis on motor depression At this point, the approach of all the physicians, nurses and members of the family needs to be mentioned It may be possible to accomplish more by a carefully planned and wisely executed program of suggestion, explanation and assurance than by the use of many drugs

In the choice of time for surgery, the physician must be alert for that time when pulse and basal metabolism have ceased to decrease and the patient has achieved the maximum of nervous sedation This is usually in the second week after beginning the use of iodine If intervention is delayed too long, there is often an increase in all the signs of toxicity, with increasing risk of a crisis If such a mistake is made, it may be the part of wisdom to postpone operation for several weeks In such a case, iodine is to be omitted while medical management is continued, after an interval during which a stable condition has been attained, iodine is again tried The chances of a second remission are less favorable The iodine acts by temporarily diverting the thyroid to storage of the hormone in the acini with less release into circulation When storage has reached an approximate maximum, the time for operation is optimal This must be determined by clinical judgment based on the factors mentioned pulse basal rate and nervous stability Weight increase is helpful, unless the undernutrition regime is employed

other reason for confinement to bed The doses must be measured and should be large enough to secure prompt results After the first course, a period of at least six weeks should intervene before the efficacy of the treatment is estimated This allows the tissue result of irradiation to appear and the effects of thyroxine excess to disappear The reason for waiting such a long time may best be explained by pointing out that after administering a single dose of thyroxine to a patient with myxedema, at least one month is required until the basal metabolism returns to the previous steady state" (See the discussion under the use of thyroid in myxedema, below) Successive series of irradiation to the thyroid are employed until the clinical evidences and the basal metabolism tests show that control has been achieved Results appear more slowly by this method than with surgery, but the after-results are good statistically

A new type of medical management for thyrotoxicosis has been tried in the last few years, based on the discovery that continued oral administration of a series of sulfur-containing compounds, most important of which is *thiouracil* will inhibit the formation of thyroxine in the thyroid gland If the therapy is intensive enough and continued for a few months thyrotoxicosis can be converted into myxedema Dosage required is approximately 0 2 Gm three times daily, preferably at about eight hour intervals The mechanism of action appears to be a block opposed to the entrance of iodine into the thyroid gland Therefore the time interval after beginning therapy until

the symptoms of fever, tachycardia and anxiety suggest a critical state, these measures are all the more urgently needed Additional measures employed are sedatives and ice-packs The intravenous use of iodine has never been shown to be helpful, and with increasing evidence that the iodine acts merely by temporarily stopping the liberation of thyroid hormone into the circulation, the emergency use of larger doses of iodine to stop a crisis seems futile and is now being abandoned For sedation, there should be no hesitation in the use of opiates to reduce the anxiety, the increased restlessness and the consequent strain on the heart The usefulness of ice-packs is in the control of fever, which is the guide as to need for its continuance When fever has dropped to ordinary limits, the commoner features of postoperative therapy will usually suffice It is thus evident that far more can be done to prevent than to treat the thyroid crisis The appearance of this state is evidence that preparation was inadequate for the operation

Irradiation of the thyroid has grown in favor in the past decade and is especially recommended for those cases in which cardiovascular or other complications increase the risks of anesthesia and surgery The best preparation for irradiation is not so definitely understood, but the use of iodine rest and high calory diet seems just as important as when surgical treatment is used Delay for evidence of remission is not needed if the diagnosis is definite, although a remission is of great diagnostic assistance at times Irradiation may be carried out on ambulatory patients if there is no

grave risk of sepsis This depression of formation of white cells may occur early in the course of treatment or not until after many weeks during which there was no hint of a toxic reaction Therefore it is considered essential that continuous observation of the white blood cell count be maintained as long as thiouracil is in use Discovery of granulocytopenia calls for immediate suspension of the drug and every effort to protect the patient against infection until the white cell count has returned to normal

With the brief background of experience the uncertainties involved and especially the toxic manifestations, it is necessary that use of thiouracil and of other less extensively investigated drugs, be considered an experimental procedure for some time further It is hoped that similarly active but less toxic drugs will be found in the search which is already under way

One of the most dramatic aspects of the thyrotoxic state is *exophthalmos* The excess of thyroid hormone does not produce this condition It often becomes worse after thyroidectomy especially if the patient has deficient thyroid function The currently accepted theory is that the thyrotrophic hormone acts on cervical sympathetic ganglions from which nervous impulses pass to the orbital muscles, leading to propulsion of the orbit and ultimately to permanent changes in the tissues which maintain the exophthalmos Intraorbital myxedema only adds to this process Since the production of thyrotrophic hormone is inhibited by thyroid hormone its use has been found to help in the control of exophthalmos The obvious paradox, that

the basal metabolism drops to the normal level will depend upon the amount of preformed thyroid hormone already stored in the gland In patients with large adenomas or in those who have received recent iodine treatment, this time interval may amount to several weeks or a few months

Thiouracil therapy may be used to secure the remission preceding thyroidectomy or possibly may constitute a means of medical management in itself The action is purely temporary, but it can be maintained as long as the drug is used Some trials have produced results suggesting that after a period of induced remission in the toxic state, the thyroid may regain a normal plane of activity which may be maintained indefinitely without therapy This has been known to occur under other types of medical management There is never any certainty how long a remission will last

In many patients under treatment with thiouracil, the thyroid enlarges notably This is believed to indicate continued stimulation to hypertrophy by the thyrotrophic hormone of the anterior pituitary Such a sequel will provide a further reason for planning on thyroidectomy after preparation of the patient with thiouracil Some surgeons feels that there is an advantage (less vascularity) gained by administration of iodine in addition to thiouracil

The added risks produced by thiouracil therapy are a variety of toxic manifestations attributable directly to the drug In addition to rashes, the most important and dangerous reaction is granulocytopenia, which may progress to complete agranulocytosis with its

if necessary to obtain the results desired There is no evident reason why it need be given in divided doses daily, since the action of the hormone is slow

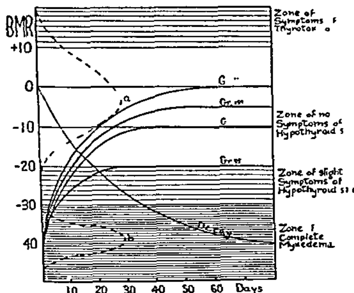


FIG 12—Approximate relationships between metabolic levels symptoms and thyroid rations Dosage is indicated in grains of thyroid U S P given once a day The curves so labeled indicate what may be expected as calorigenic response when the several rations are given to patients with complete myxedema. Curve labeled Decay' indicates metabolic response that may be expected when one discontinues administration of thyroid to patient with myxedema whose metabolic rate was maintained at standard level or when one completely extirpates thyroid gland of person with standard metabolic rate The frequency curves plotted against the basal metabolic rate at the left, are (*a*) for persons with no thyroid disease and (*b*) for patients with spontaneous myxedema. (After Means J H and Lerman J *Arch Int Med* 55 1-6 January 1935)

and long continued The diagram (Fig 12) shows the slow increase and still slower decrease in the action of a single dose of thyroid From the use of such material daily, it is inevitable that one sees cumulative

exophthalmos develops during a period of thyrotoxicosis, when there is believed to be an excess of circulating thyroid hormone, remains unexplained If exophthalmos becomes increasingly severe despite the control of thyrotoxicosis and the administration of maximally tolerated doses of thyroid, surgical intervention such as orbital decompression may be required to conserve the integrity of the eyes

The treatment of *hypothyroidism* in any form requires the use of dried thyroid There is no advantage to the use of the purified thyroxine which must be given in alkaline solution, whether by mouth or intravenously There is no official "thyroid extract" Unstandardized thyroid preparations introduce several hazards to successful therapy The thyroid should be prescribed as 'Thyroid, U S P," or 'Thyroid, B P," in order to assure the obtaining of a standardized preparation Attention should be called to the far lower potency of B P (British Pharmacopoeia) standard thyroid If it is to be employed, dosage must be about five times as great as with U S P Thyroid Wide use of one brand of standardized thyroid of still higher potency (Parke, Davis and Company) makes its activity worthy of special attention It is difficult to compare results of this brand with that of the U S P tablets Therefore, it is imperative that the physician use only one type of standardized thyroid for a given patient if he desires consistent results Thyroid tablets vary in content from 6 to 130 mg (0 1 to 2 gr U S P), and the daily dose may be as high as 1 Gm (15 gr)

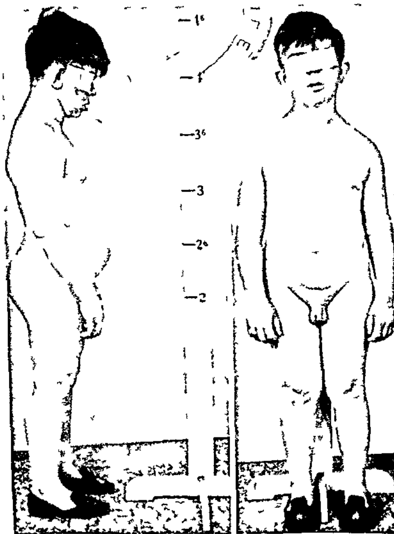


Fig 13—Cretinism Age 20 54 in tall 106 lb Dulness noticed since second year at which time thyroid therapy was begun but never regularly sustained First used words at 4 but unable to talk intelligibly at 20 Walked alone at 6 Family history negative Intelligence quotient 0 22 Basal metabolism 19 per cent below prediction, with cooperation difficult Bone age 10 11 years epiphyses still open Thyroid dose was 2 gr daily at first then 4 gr after six months 6 gr was tolerated Speech attitude weight intelligence all improved during these six months

action It requires from one to three months of daily dosage at a given level to attain the maximum effectiveness as measured by the basal metabolism Still longer periods are required to secure all the clinical benefits in cases in which chronic hypothyroidism has left deep seated stigmas in the tissues Therefore the program of therapy must be carried on slowly, with patient perseverance, and the results can only be judged in terms of months

There is a risk in the too rapid elevation of the basal metabolism by the use of thyroid in a myxedematous person The increasing metabolic needs impose a demand for increased minute volume of circulation, which in turn means more work by the heart The myxedematous heart is in a state of muscular weakness Sudden imposition of this increased demand may produce congestive failure If the increased metabolism is brought about gradually, the nutritive condition of the heart muscle improves *pari passu* and the circulation keeps pace with the need The beginning of therapy should therefore be with doses as low as 65 mg daily, and increases should be made only as clinical results are observed Furthermore, no patient using thyroid for such conditions or any other should be dismissed from medical supervision lest gradually he build up an excessive dose and produce a state of thyrotoxicosis Clinical examination at intervals of at least a few months is essential even after the maintenance level has been reached (See Figure 15)

Accessory treatment often requires the use of limited caloric intake to control the obesity which may

accompany hypothyroidism This suggests the use of thyroid to assist in more rapid reduction of *obesity* even when hypothyroidism is not of etiologic impor

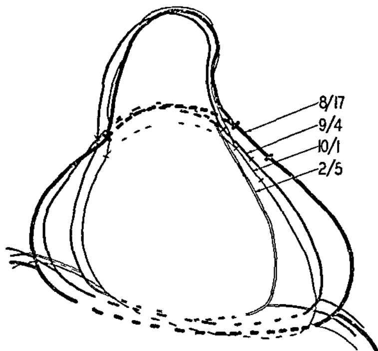


FIG 15—Orthodiagram of patient with myxedema showing reduction in heart size under thyroid therapy From 51% above normal to only 8% above in six weeks 2% above normal after six months Progressive improvement secured by sustained therapy

tance The practice is common but is fraught with dangers unless supervised by a clinician who can watch for evidence of thyrotoxic symptoms This type of therapy is frankly the production of a mildly toxic state to accelerate removal of excess weight It will not be successful without dietary limitation Thyroid



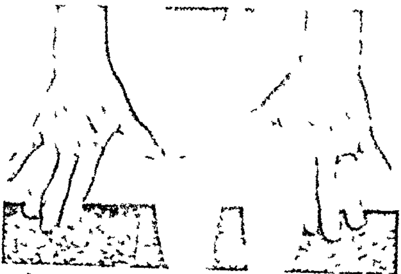


Fig 14—Myxedematous woman 50 who had complained eight years of deafness amblyopia facial edema weakness nausea vertigo constipation coldness paresthesias and joint pains Besides sparse dry hair expressionless face pallor and obvious weakness there were sluggish reflexes arteriosclerosis enlarged heart and tendency to hypotension Basal metabolism variable as low as —27% Whole blood cholesterol 330 394 mg per 100 c c Under thyroid therapy basal rate and cholesterol returned to normal levels Weakness anorexia and hypotension were further relieved by adrenal cortex administration for several weeks Incidentally with *such supportive* therapy patient had uncomplicated convalescence from scarlet fever contracted during period of study

study has been the demonstration that most colloid goiters and much thyrotoxicosis can be prevented by an adequate intake of iodine throughout infancy and childhood At least in all regions with endemic goiter, it should be the practice to use only salt which has had iodine added to it after the removal which occurs in refining, i e, so-called iodized salt The only important risk in the use of this salt is that the intake may be inadequate Therefore if there is any doubt, the use of weekly doses of 10 mg sodium iodide is advised The most convenient form is in chocolate coated tablets containing the iodine in organic compounds The advantage of these synthetic compounds is that they do not become moist on exposure to the air This procedure may well apply to all children up to the completion of adolescence

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REFERENCE FOR FURTHER READING

J H MEANS The Thyroid and Its Diseases (Philadelphia J B Lippincott Co 1937)

therapy for simple obesity ought to be used much more sparingly and certainly never by unsupervised laymen (See Chapter 14, "Obesity")

The employment of thyroid in treating obesity from obscure causes, dryness of the skin, menorrhagia, low fertility, nephrosis, etc, is an empiric use of an active gland product Clinical results have justified such procedure in many cases The precautions mentioned for treatment of hypothyroidism apply here

Attempts to reduce obesity by use of thyroid in moderate doses are seldom strikingly successful In view of the low efficiency of thyroid for this purpose, its great vogue in the recent past is surprising

Prognosis

The cretin and myxedematous patient will require continual treatment throughout life The doses often have to be varied Sometimes the need is greatly increased during periods of rapid growth or during long continued infections In general, the need for thyroid decreases after adult life is reached

The end-results of surgical or irradiation therapy for thyrotoxicosis are qualified by the underlying personality type (Graves type) *in many patients* and by the occurrence of cardiac damage preceding the treatment in older patients especially These factors call for a systematic program of medical supervision, adapted to the individual need

Prevention

One of the most pleasing features of endocrine

high serum calcium are explained Conversely, reduced hormone function will be followed by accumulation of serum phosphorus and consequently tendency of phosphorus to enter the bony reservoirs, in which case calcium must also enter In this process there will be elevated serum phosphorus and depressed serum calcium In the first case bones will become decalcified, in the latter case, abnormally densely calcified Albright who developed this theory has since shown it to be inadequate, even though true Parathyroid action influencing serum calcium seems to occur directly as well as via the serum inorganic phosphorus level Either hypocalcemia or hyperphosphatemia is thought to stimulate parathyroid secretion of more hormone The metastatic calcification which takes place in individuals with a long standing hyperparathyroidism is probably due to a damage to soft tissues following the persistently low serum phosphorus or other metabolic disturbance, after which calcium deposits as it frequently does in sites of injury

Diagnosis

The syndromes of *hyperparathyroidism* include osteitis fibrosa cystica, diffuse osteoporosis of certain types, renal calcinosis or recurrent stone in the urinary tract, metastatic calcifications There may well be other manifestations not yet recognized The diagnostic differentiations of these conditions from the other types of bone cyst, osteomalacia from other causes other types of renal stone or nephritis without

Chapter 6

PARATHYROIDS

Function

There is still doubt as to the existence of a factor from the anterior pituitary which controls parathyroid activity The secretion from the parathyroids is known only in impure form, but the extracts have the ability to elevate total serum calcium and depress serum inorganic phosphorus concentrations Deficiency of parathyroid function is followed by abnormally low calcium and high phosphorus concentrations Overactivity of the glands with adenomas or diffuse hyperplasia leads to mobilization of calcium from bones, abnormally high serum calcium content, metastatic calcium deposition in soft tissues, calcinosis in the kidneys being particularly dangerous and sometimes recurring stones at different parts of the urinary tract The exact chemical and physiologic mechanisms involved in the control of minerals by the parathyroid are not known One of the simplest ways to view the parathyroid function is to consider the primary activity of the hormone as facilitating excretion of inorganic phosphorus by the kidneys Overfunction will lead to depletion of serum phosphorus, with resultant mobilization of this element from the bony reservoirs Necessarily, this will involve mobilization of calcium and thus the low serum phosphorus and

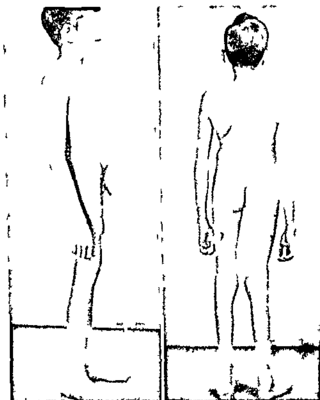


Fig 16—Hyperparathyroidism Boy 13 had been in sanatorium four months suspected of tuberculosis Emaciation muscular weakness extreme relaxation of joints permitting fantastic contortions recent hip and knee pain Weight 66 lb 20 per cent below expectation for 58 in height X rays showed osteomalacic disease and slipped epiphysis of right hip Blood calcium varied from 10 8 to 11 4 mg phosphorus from 4 3 to 4 6 mg per 100 c c There had been one fracture from trivial injury The conclusion that hyperparathyroidism was the cause of the osteomalacia was based on calcium excretion studies during which the daily urinary loss of calcium was 0 613 Gm during an intake of 0 6 Gm fecal calcium loss undetermined would add to significance of this negative balance Surgical exploration of thyroid region failed to reveal enlargement of parathyroids One normal appearing gland was removed without clinical change

calcium deposition would require more space than is available (See Figure 16) Frequently the methods are technically elaborate, requiring the estimation of calcium and phosphorus in both blood and urine

The fundamental diagnostic feature is that when a patient with hyperparathyroidism is maintained for several days on a diet providing as little as 0 2 Gm calcium daily the urinary calcium loss will continue distinctly greater than this amount Fecal calcium loss will further augment the negative balance Such a negative balance is the most cogent evidence, reenforcing the low serum phosphorus and high serum calcium levels, for hyperfunction of the parathyroids (Consult papers of Albright *et al* in "References for Further Reading' for details)

Hypoparathyroidism leads to tetany, with high blood phosphorus and low calcium concentrations The diagnosis by observation of laryngeal stridor, spontaneous carpopedal spasm or the induced spasms of the Chvostek Trousseau and Erb tests, plus the paresthesias, is confirmed by finding calcium in the serum below 8 mg per 100 c c (normal, 10-12 mg) Later findings include cataract formation, usually multiple Tetany ought to be suspected in all cases of laryngeal stridor (except diphtheria), with convulsive movements, with presenile cataracts and with tingling paresthesias of indefinite origin The parathyroid underfunction may result from trauma at thyroidectomy, or it may be idiopathic Epidemic or infectious types of tetany are apparently rare in North America

Therapy

For *hyperparathyroidism* it is urgently necessary to stop the process as soon as possible to protect the bones from deformity and most of all to avoid further renal damage from calcium deposition When the diagnosis has been made probable surgical exploration of the glands is justified, with removal of adenomas or resection of a large share of hyperplastic gland when that is found The use of x-ray is of interest, but it does not permit diagnostic confirmation by tissue study in doubtful cases The value of irradiation in this field is still under investigation High calcium feeding to protect the bones is contraindicated, because of the tendency to calcinosis in the kidneys, until the condition has been brought under control Immediately after surgical intervention tetany may be precipitated, and means must be at hand for its emergency control (Albright *et al*)

Tetany presents both acute and chronic problems Acute attacks can be relieved by intravenous injection of calcium salts The most efficient of these is calcium chloride which is used with some risk of thrombosis unless it is given in dilutions of about 0 5 per cent in normal saline The dose should be at least 1 Gm The aqueous solutions of calcium gluconate available in 10 per cent solution may be given intravenously with safety and with almost as prompt effect Parathyroid extracts, of which there are three preparations (Parke Davis Lilly Squibb) of equal potency give more sustained results but the elevation of calcium concentration by this means does not ap

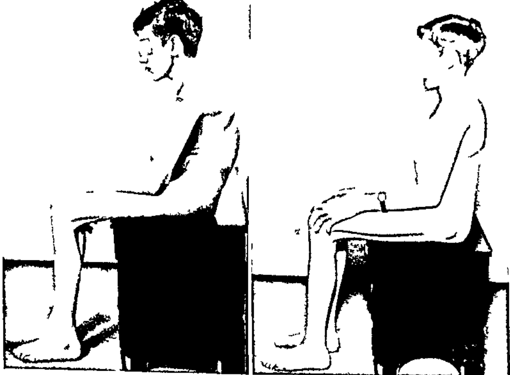


Fig. 17 (left) —Same case as preceding before treatment
Fig. 18 (right) —Same case after irradiation of the remaining parathyroids with two series of four treatments each 150 r per treatment overactivity of parathyroids was arrested Note improvement in posture possible after arrest of hyperparathyroidism

TABLE 1

Low Phosphorus Diet (from Ellsworth)

Eat no foods except those listed

Breakfast	1 serving fruit 1 strip crisp bacon 1 small slice toast with butter and jam or honey
Luncheon	1 small serving potatoes 2 servings vegetables 1 serving fruit or gelatin with fruit 1 small slice bread and butter
Dinner	1 oz. chicken 1 serving vegetables lettuce salad 1 small slice of bread 1 serving fruit or small custard

Fruits	Vegetables
Apples (1)	Asparagus
Bananas (1)	Beets
Cranberries	Cabbage
Grapefruit (1½)	Carrots
Grapejuice (½ glass)	Celery
Lemon	Cucumbers
Cantaloupe (½)	Lettuce
Orange (1)	Winter or summer squash
Orange juice (½ glass)	Tomatoes
Pears (1)	Turnips
Peaches (1)	Radishes
Strawberries	
Watermelon	

These may be added to diet in fairly large amounts

- Butter and salad oil
- Honey
- Jam and jellies
- Sugar
- Gelatin
- Egg white
- Shrimp canned or fresh
- Salt and pepper
- Tea and coffee
- Cream (only in small amounts)

In place of 1 oz chicken (cooked) you may use

- 1 oz halibut or haddock
- 3 oz oysters
- 1 oz crab flakes

Note—See appendix to Shelling The Parathyroids in Health and Disease, for detailed menus.

pear for a few hours This slow and maintained effect gives rise to the phenomenon of cumulative action, and the dosage must not be more frequent than daily Doses of 50 to 100 units are employed

The plan for sustained treatment of tetany depends on whether it is an acute problem after trauma incident to thyroidectomy or chronic from destruction or absence of the gland Until the case is shown to be chronic, the assumption of acute tetany is justified The therapy for acute cases involves the use of a high calcium and low phosphorus diet, which is essentially one low in meat, milk and egg yolks and high in leafy vegetables (Table 1, from Ellsworth) Calcium intake is fortified by oral use of chloride, lactate or gluconate These salts decrease in their efficiency per gram in the order named They can be taken orally in doses of 1 to 2 Gm three times daily Absorption is best when the salts are given half an hour or more before meals, with copious water It is better to have the salts well dissolved, not taken in tablet form If the calcium chloride is used it may be dissolved and the taste partially concealed in a vehicle such as Syrup Glycyrrhiza, in this way 25 per cent solutions can be taken orally, 1 teaspoonful thus yielding 1 Gm Acute emergencies of tetany may be met with intravenous injections of calcium salts and, if frequent, with use of parathyroid extract

When the therapy has to be extended beyond a few weeks at most, the gland extracts prove to be of decreasing efficacy, for reasons still unknown It becomes necessary to rely on the dietary measures al

absorption In view of this it seems unwise to use thyroid, especially since it is now possible to relieve tetany by vitamin D or A T 10, which affords a probable physiologic substitute for the missing hormone

Prognosis

The tetany after thyroid surgery is usually temporary, vanishing with or without treatment in a period of not over one month It is often so mild that it is overlooked On the other hand, it may lead to fatal laryngospasm Aside from this risk, the prognosis is excellent for complete recovery If improvement is not progressive in the first month the prognosis is for chronic tetany similar to the idiopathic types In the chronic cases the condition lasts indefinitely, but in almost all cases its manifestations can be controlled with oral therapy alone Prevention of cataracts by sustained treatment as outlined has not been proved, since the program outlined has been in use for only a few years and the cataracts do not always appear early in the course of the disease

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ready mentioned and the oral use of calcium salts and to reenforce these measures by the use of irradiated ergosterol For this purpose the usual forms of vitamin D will serve, although doses must range from 50,000 to 500 000 I U daily for complete control The development of a special irradiation product named dihydrotachysterol, was considered particularly favorable, for this compound has been said to have less antirachitic activity but more ability to augment phosphorus excretion than the vitamin D molecules This claim is still being debated Clinical trials for the last few years indicate that either vitamin D or dihydrotachysterol, if given in adequate doses, will provide complete control of tetany By such methods rigorous limitation of phosphorus intake is not urgent Calcium intake should be augmented Control of therapy by serum calcium determinations at least every few months is important Dihydrotachysterol is marketed under the trade name 'Hytakerol," produced solely by the Winthrop Chemical Company It is also spoken of as A T 10 since it was the tenth (A)nti (T)etanic drug prepared by Holzt, the discoverer The daily doses of Hytakerol" vary from 5 to 20 drops of the oily, dilute solution in use Vitamin D is now available in capsules containing 50,000 I U

There has long been evidence of some usefulness of thyroid in management of chronic tetany, this has been explained by Aub as due to mobilization of calcium In 1939, evidence was published by Althausen Kerr and Stockholm to show that thyroid causes negative calcium balance by interfering with calcium

Chapter 7

MAMMARY GLANDS

Function

The obvious function of lactation is achieved only after development of the duct system under stimulation by the estrogenic hormone and of the acinar tis sue by progesterone, both contributed by the ovaries During pregnancy, these substances are secreted in greater amount by the placenta As a consequence, typical mammary growth follows, but lactation does not appear until shortly after delivery The sharp reduction in the supply of progesterone post partum is followed by secretion of an increased amount of a pituitary material which is mammatrophic, and this leads to copious lactation The identity of this pituitary hormone is still uncertain, but it is called "prolactin There have been few clinical trials, but these have shown some promise There is still much skepticism about the clinical use of this hormone The inhibition of lactation by estrogenic materials has been attempted in many clinics, but the results suggest that the chief result of the therapy is to reduce painful engorgement of breasts

Therapy

The clinical indications for use of mammatrophic hormone would seem to be delayed or absent lacta

FULLER ALBRIGHT, E BLOOMBERG, T DRAKE, and H W SULKOWITCH Comparison of A T 10 (Dihydrotachysterol) and Vitamin D on Calcium and Phosphorus Metabolism in Hypoparathyroidism J Clin Investigation 17 317-329, May, 1938

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At present, the relationship of endocrine stimuli to the condition of cystic disease in the breast is far from clear Attempts to treat the nonmalignant lesions of the breasts with estrogen, progesterone or the various unstandardized ovarian materials are in an experimental stage The different clinical approaches to this problem do not appear to be rationally consistent with each other although clinical successes are reported

Since the ovarian hormones, estrogen and progesterone are the physiologic stimuli for the growth of the breasts, it is probable that these same hormones will stimulate the growth of breast neoplasms Therefore before clinical use of these materials is attempted it is wise to examine the breasts to make certain there are no signs of tumor growth Clinical doses of estrogen employed for the proper management of the climacteric are far too low to give rise to neoplasms in otherwise healthy breasts The carcinogenic action of such hormones in experimental animals has followed enormous doses as compared with those used for treatment of women It is not infrequent that the treatment of the climacteric is marked by tenderness and swelling of portions of the breast tissue This can be quickly alleviated by a reduction in dosage of the estrogen employed usually without any sacrifice of the relief from climacteric symptoms which is the goal of therapy

The employment of large doses of estrogenic hormone to prevent or to stop mammary secretion immediately *post partum* is no longer considered as suc

tion post partum, or deficient lactation which is still more frequent Potent preparations are not yet on the market

Since the growth and development of the breasts depend on the stimulation by estrogen and progesterone, it is illogical to expect the pituitary mammatrophic substance to influence the size of the breasts There has been some clinical evidence that the prolonged use of a combined program of estrogen and progesterone therapy might be helpful in securing growth of a larger amount of breast tissue This may be the more important procedure in women who have previous history of inadequate lactation or whose breast development is small in a well advanced stage of pregnancy On theoretical grounds, it seems that intensive estrogen and progesterone therapy before pregnancy might not be wise owing to inhibiting effects on anterior pituitary function The result is apt to be irregularity of menstrual cycles but such irregularity is temporary

The demonstration by MacBryde that application of estrogen in ointment to the breasts leads to mammary growth is of interest, but it is to be noted that this increased size of breasts was not maintained after the therapy was stopped It would therefore be appropriate during pregnancy but of questionable value otherwise

There is no definite clinical program which can be applied to the annoying problem of excessively large breasts Whether this condition results from excess of ovarian hormones or other disturbance is unknown

Chapter 8

PANCREAS

Function

The existence of a pituitary factor which stimulates development and activity of the pancreatic islands of Langerhans is debated Since hypophysectomy does not cause pancreatic atrophy or diabetes, the significance of such a factor is not of paramount importance as in the case of adrenal cortex and gonads, or even of the thyroid The function of the islands is to produce insulin a water soluble substance resembling a fragment of a protein molecule, which acts as catalyzer for dextrose in such processes as oxidation, conversion to fat or to glycogen and possibly the other numerous uses to which this sugar is put The rate of supply of this hormone is therefore one of the most important factors which determine the level of the blood sugar Insulin secretion is increased by hyperglycemia and by vagal stimulation Factors tending to raise blood sugar concentration are absorption from the gut, glycogenolysis from muscles and more especially the liver and conversion of protein to sugar Increased secretion by anterior or posterior pituitary, thyroid or adrenal cortex or medulla tends in the direction of increase in blood sugar level Those factors tending to lower the blood sugar level are the oxidative use of

cessful as formerly thought. Such treatment has served to reduce the painful engorgement of breasts in many women Doses of 25,000 I U or more are injected one or more times daily for a very few days, at the same time that the conventional measures are employed to stop lactation

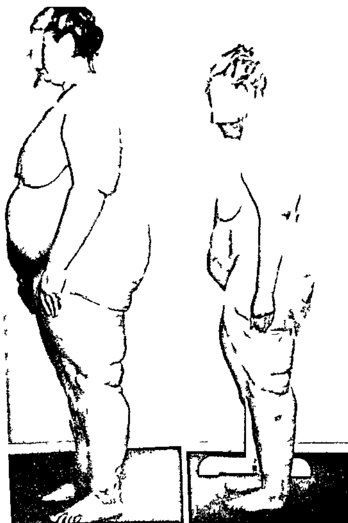


Fig 19—Obesity resi tant to urgent desire to reduce with vigorous hunger between meals Sugar tolerance test showed h pogl cemia of 60 mg per 100 c c in third hour Loss of 80 lb n 9 months without hunger on 930 calorie diet with carbo hydrate about 90 Gm daily

dextrose, conversion to fat or glycogen for storage, conversion to lactose in the secreting mammary gland and a number of processes which are quantitatively less important from the point of view of the total amount of sugar used, even though they are necessary to normal function of the body The insulin action is to facilitate this group of processes by which sugar is used and stored Excretion of sugar by the kidney reduces blood sugar concentration only in cases of renal glycosuria or with abnormally high blood sugar levels, as in diabetes mellitus or after temporary excesses of absorption or glycogenolysis

The processes by which insulin is extracted from the pancreas make it possible that the purified extract is not the actual hormone normally active in the intact body but a more rapidly acting fraction derived from the hormone itself This is analogous to the problem of thyroxine and its peptide union with protein material in thyroglobulin The recent achievement of slow acting insulin preparations by uniting insulin to protamine and zinc or to histone or globin is an attempt to secure intensity and duration of action more like those of the hormone as secreted by the pancreas

Diagnosis

Hyperactivity of the pancreas is encountered in cases with adenoma of the gland or with diffuse hyperplasia, or with no morphologic changes The diagnostic evidence of overactivity of the pancreas is relatively low blood sugar concentration, often with the symptoms produced by overdosage with insulin in dia

betics The complaints may be of hunger, tremors, sweating, nervous irritability in acute attacks, headache, or there may be disorientation resembling drunkenness, or convulsive phenomena and, in long continued cases, coma The diagnostic problem is rendered more difficult because the milder symptoms and moderate lowering of blood sugar can be caused by accentuation of the rate of sugar utilization and disturbances of storage such as occur in thyrotoxicosis or some hepatic diseases There is no dependable method for proving an excessive production of insulin Such excess production is inferred from low blood sugar levels without other obvious and adequate reasons Pancreatic tumor should be suspected whenever the fasting blood sugar level is repeatedly below 50 mg per 100 c c (Folin-Wu method) This condition of recurrent hypoglycemia should be thought of and sought for by sugar tolerance tests in cases of obesity especially when there is a marked appetite for food between meals Discovery of such a basis for excessive hunger and extra food intake may lead to greater facility in reducing such patients (Fig 19)

Therapy

Hypoglycemia may be treated by the use of frequent feedings with liberal amounts of carbohydrate foods However, some individuals respond better to the use of the high fat low carbohydrate diets in the conventional three meals The efficacy of the latter regime is explained as reducing the stimulation to the sugar utilization mechanisms with consequent reduced

gram calls for the use of a diet which is adequate in caloric content for the needs of the individual The proportion of carbohydrate and fat is usually reversed from habitual diets, so that the carbohydrate intake will be within the capacity of the body to utilize without glycosuria If this is impossible without reducing the intake to the point where starvation ketosis ensues the only clinically satisfactory management is with the hypodermic administration of insulin Dosage is adjusted by trial and error to attain freedom from ketosis at least, maintenance of weight equilibrium at the optimum for the height and age and usually also freedom from glycosuria The details of the diagnostic and therapeutic procedures involved will be found in Chapter 9, on diabetes mellitus

Nonspecific Therapy with Insulin

It may be helpful to reduce blood sugar concentration with insulin to stimulate a hunger reaction and improve food consumption This has often been helpful in cases of *anorexia nervosa* The dose should vary from 5 to 25 units with gradual increases until results are obtained The timing of the injection before the meal is determined by trial, with the aim of securing the hunger reaction at appropriate intervals This usually means that the injections are to be given 20-45 minutes before eating

Use of insulin to produce profound hypoglycemic shock in patients with mental disturbance represents use of a hormone in tremendous excess for pharmacodynamic purpose Apparently there is a chemical al-

production of insulin during absorption The presence of a moderate amount of fat in a meal tends to delay passage of the food along the upper part of the digestive tract, thereby prolonging the absorption and preventing hyperglycemia and hypoglycemia alike This approach is particularly helpful in cases of postprandial hypoglycemia, i e, symptoms occurring one to four hours after meals If these dietary means do not help, and especially when the symptoms are acute and progressive, surgical exploration of the pancreas is justified Tumor cannot be diagnosed with certainty by other means than the blood sugar studies and the progressive tendency despite therapy

Deficiency of Insulin

Diabetes mellitus is a clinical syndrome probably caused by any one or more of several disturbances in the group of processes which are involved in sugar metabolism The diagnosis depends on a sustained inability to use the sugar rapidly enough to prevent hyperglycemia above 120 mg per 100 c c two or more hours after liberal intake of carbohydrate food When this inability is marked, the hyperglycemia leads to glycosuria Still further inability to use sugar is marked by the appearance of the ketone bodies, acetone and aceto acetic acid, in easily detectable amounts These features—hyperglycemia, glycosuria and ketosis—are the diagnostic marks and means for demonstrating the severity of the disease They do not serve to fix the etiology of the disturbance

No matter what this etiology, the therapeutic pro-

Chapter 9

DIABETES MELLITUS[1]

Diagnosis

When diabetes mellitus is suspected, the diagnosis is to be made by the use of urine and blood chemical examination If the urine gives a positive reaction with Benedict's reagent, the patient should be assumed to be diabetic until this is disproved The diagnosis may be settled by the result of a blood sugar determination Blood taken before breakfast or two to three hours after the last food should never contain more than 120 mg sugar per 100 c c Figures higher than this indicate the presence of diabetes mellitus, unless the patient has severe chronic nephritis is emotionally disturbed at the time of blood taking or has recently been treated with sugar epinephrine ephedrine or some other drug that raises the level of blood sugar Chronic nephritis will be indicated by the marked elevation of the nonprotein nitrogen in the same blood sample Nephritis and diabetes may occur in the same patient, but this problem is seldom confusing, since the blood sugar figures then are usually 200 mg or over and since the elevation of the sugar in a patient with severe chronic nephritis but without diabetes is

1 This hapte [illegible] nd usat n f the S t n f Phy ns in th GUID TO DIA ETIC P t NTS publi hed by the auth The d tary data a d m u f om th pat ent secti f the same gu d C p of th 96 page book may be o der d f om th [illegible] M d n W s at $1 35 *postpaid*

teration in the brain tissue, which interferes at least temporarily with normal function and is followed by repair, at which time return to a more normal function is hoped for There is reason to believe that repeated severe insulin shocks lead to marked disturbance of brain function, perhaps permanent changes in structure and mental activity With such possibilities insulin shock therapy should be reserved for mental states which have definitely poor prognosis when untreated

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hour sample is unduly high but returns to normal in three hours, the condition is called "cyclic hyperglycemia," but the patient does not have diabetes However, if the hyperglycemia is maintained so that the two and three hour samples are still above the upper normal of 120 mg, diabetes mellitus may be diagnosed with confidence If glycosuria occurs before blood sugar values reach 170 mg, the renal threshold is lower than usual, and "renal glycosuria" is the diagnosis

THE ACETONE TEST

When sugar has been found in the urine for the first time, there is one other test which should be made without the slightest delay, namely, the test for acetone bodies The method is given on pages 106 and 107 This is not the most sensitive test for acetone bodies, but it is the more valuable since it will not be positive unless they are present in clinically significant amounts If the test is positive, there are two facts which must be faced at once the patient will almost certainly have to use insulin in order to become free from glycosuria on a maintenance diet, and if treatment is delayed there is real danger that he will pass into diabetic coma Therefore, the finding of a positive test for acetone calls for immediate and thorough treatment. It is safer to assume that the patient is in danger of coma and to prevent this accident, than to wait for evidence of the coma The treatment is outlined on pages 107-113

If the acetone test is negative there is no immedi

seldom over 150 mg Disturbance of the blood sugar level due to emotion is temporary and is usually suspected from the behavior of the patient It may be induced by the pain or fear of the taking of the blood sample Such emotional disturbances seldom lead to blood sugar values as high as 200 mg It is, however, in just this range of blood sugar values, 120-200 mg, that mild and early diabetes is to be diagnosed with certainty by the use of the blood examination, so that a single 'borderline value' should not be trusted

THE SUGAR TOLERANCE TEST

If there is doubt, the sugar tolerance test is employed No food is taken after supper In the morning the patient receives 50 Gm glucose in a glass of water, to which is added the juice of half a lemon More water may be taken if desired Blood samples are taken immediately before the sugar is drunk and at intervals of one-half one two and three hours afterward Urine samples are collected when possible at these same intervals The urine is tested with Benedict's qualitative reagent for sugar The blood sugar values are the crucial consideration In normal persons, the concentration of sugar in the initial sample should not exceed 120, the high point should occur at the one-half hour sample and should not exceed 180 and in the three hour sample blood sugar values should again be under 120 In fact with most normal persons the blood sugar at two hours is already back to or below the fasting level The three hour sample is the most significant of all If the sugar in the half

If his total need for energy exceeded that figure, the remainder would have to be secured at the expense of protein and carbohydrate oxidation, of each of which such an individual would ordinarily be using 50 or more Gm, making available another 400 or more calories The capacity for fat oxidation is further increased by muscular exercise If for any reason the demands for fat combustion exceed the capacity of tissues to burn aceto-acetic acid, the acid accumulates in tissues, appears in significant amounts in the blood and is detectable in the urine Under these conditions part of the aceto-acetic acid is reduced to a less active substance betahydroxybutyric acid, and a further part is converted to a neutral compound called acetone These three compounds are called the ketone bodies because acetone the simplest one, is a ketone The accumulation of these materials to the point where they can be recognized by clinical tests is called ketosis The significance of ketosis is therefore merely that the liver has prepared for oxidation more aceto-acetic acid than the tissues can oxidize The occurrence of ketosis is a signal to the clinician that more carbohydrate must be provided (in fasting) or made available for oxidation by injection of insulin (in diabetes)

Of these ketone bodies acetone is most easily recognized by the urine tests and by its presence in the expired air It is sometimes convenient to use the test for acetone in the breath as a guide to the use of insulin in the treatment of coma This method has certain complicating difficulties but in trained

ate danger of coma and it is perfectly safe to take time to try to control the diabetes by dietary measures alone The chances are that at least four out of five such patients will not need to use insulin The acetone test thus offers a means by which the physician can say with fair certainty on the first examination whether or not the patient will have to plan on using insulin

The significance of acetone bodies in the urine is that the capacity of the body to burn fat has been overtaxed Normally, the fuel of the body is made up of a mixture of protein, carbohydrate and fat Whenever the supply of carbohydrate is low, as in fasting or there is impairment of carbohydrate oxidation, as in diabetes mellitus, protein and fat must be called upon in proportionately larger amounts The protein supply is limited whether from food, surplus stored protein or the breakdown of tissues The body has ordinarily very large stores of fat available for just such purposes As an early step in the combustion of fat, the liver produces from the fatty acids several molecules of aceto acetic acid This acid is very reactive and can be oxidized in muscles, etc, as an excellent source of energy There is a limit to the amount of aceto acetic acid, which can be burned per hour per kilogram of tissue just as there is for glucose The limit for aceto-acetic acid is approximately the equivalent of 3 Gm fat per day per Kg This would mean that a man weighing 80 Kg could burn 240 Gm fat daily while at rest, deriving therefrom 2 160 calories of energy

the name of U S P Solution of Ferric Chloride

To 5 c c urine in a test tube, add the ferric chloride solution a few drops at a time until no more change is observed by the addition of the last drops The cloudiness which usually appears is not the important matter A deep wine red color appears if acetone is present If salicylates, such as aspirin, have been taken recently, a similar color will appear even though there is no acetone The color caused by acetone fades on heating, while that from the medicines is not changed To make sure that the color comes from acetone place a tube with the wine red test in boiling water for five minutes If the color fades noticeably as compared with an unheated tube, there was acetone in the urine

Therapy

TREATMENT OF COMA

The following needs must be met in diabetic coma The urgency of the need is in approximately the order in which the factors are listed (1) bed rest, (2) insulin, (3) water, (4) alkali (5) warmth, (6) relief from constipation

The plan of treatment to be outlined is applicable alike to patients in complete coma, i e unconscious, with air hunger low temperature dehydration and very soft eyeballs, and to those patients with marked evidence of acidosis in whom the onset of coma is feared In any case the patient is to be confined to bed with constant attention by a nurse if possible until 24 to 48 hours after the evidences of the emergency are past Unduly early rising from bed puts a

hands it is excellent The reagent is a cyanide of silver and mercury, and it contains strong alkali, therefore it is harmful to the skin or mucous membrane It is also expensive and deteriorates in a few months The technic is given by Paul Roth in the *Journal of Laboratory and Clinical Medicine* 11 275, December, 1925 The adaptation given by Wallhauser in the *Journal of the American Medical Association* 91 21, July 7, 1928, is not as dependable for practical application The apparatus for Roth's technic can be made from test tubes, or it may be purchased with the reagent from the Central Scientific Company, Chicago

The ferric chloride test for acetone given below is often spoken of as a test for diacetic acid This is correct But acetone never occurs without diacetic acid in the body, and hence the ferric chloride test is for "acetone bodies" They always occur together and have the same significance The commonly used nitroprusside tests for acetone react to both acetone and diacetic acid and are more sensitive than the ferric chloride It is well to have the less sensitive test, so that positive reactions are always significant It is possible to have a positive nitroprusside test with a negative ferric chloride result, which means that there is a small amount of acetone present in the urine, not indicative of danger from coma

Test for Acetone—Whenever sugar appears in large amounts, it is well to know whether there is acetone in the urine Use the ferric chloride test The reagent can be secured from any pharmacist under

therefore advisable Besides the undesirability of the reactions, the fundamental need of the comatose diabetic is to be able to burn enough sugar so that he may not only support life but also burn up and rid his body of the accumulated acetone bodies, which are toxic Both the prevention of insulin reactions and the burning of the acetone bodies calls for the use of frequent supplies of sugar This is to be furnished with sufficient liberality so that the blood sugar content is not allowed to fall below normal levels The simplest way to make sure of an adequate supply of sugar is to allow some glycosuria until all acetone is gone There are several routes available for administering the necessary sugar

Parenteral Feeding—If the patient is not vomiting and is able to swallow fluids give orange juice sweetened with sugar Orange juice is considered a 12 per cent solution of dextrose, and common table sugar is added The total dose of sugar given in this way should be 20 Gm for each 10 units of insulin One half glass of orange juice plus 2 teaspoons of sugar will provide 20 Gm sugar This use of orange juice and sugar should be continued as long as insulin is being used to bring ketosis under control

If the patient cannot be depended on to swallow and retain fluids one must resort to introduction of fluids by rectum, under the skin or into the vein The first is simplest, the last most certain For any one of these three prepare a 5 per cent solution of dextrose (glucose) For rectal use it need not be of high purity nor need it be sterilized For subcutaneous or

strain on a temporarily crippled and overworked heart, which may result disastrously

Insulin should be administered as soon as the diagnosis of severe diabetic ketosis is made The initial dose varies from 20 to 50 units Subsequent doses are given at one to three hour intervals, the dose varying from 10 to 20 units The smaller doses are used for small patients or for those not in extreme clinical danger This routine is kept up day and night until the acetone test is negative Therefore the urine should be tested before each dose of insulin is to be administered When ketosis stops, the insulin administration may be changed to three doses, given before the meals These three doses may be the same size, and their total will be somewhat less than the amount needed during the preceding 24 hour period when the emergency was being brought under control Exact daily dosage must be determined by trial during the days that follow

The condition of diabetic ketosis with or without coma is always associated with a high blood sugar concentration Insulin therapy as outlined will reduce this sugar rapidly and it may bring it down to levels which produce "reaction" or "shock" This is an unpleasant temporarily disabling and sometimes dangerous complication of the use of large doses of insulin Later in the treatment it can be guarded against because the symptoms are recognized by the patient, who is thus warned of the developing reaction At first the patient is too ill to be instructed in these symptoms Means for preventing reactions are

vere insulin reactions When, as in ketosis, fluids are also needed, the sugar is diluted before injection The dilution may be made with sterile distilled water or normal saline A 5 per cent solution of dextrose is almost isotonic with blood and may therefore be in jected safely, or it is equally safe to mix 5 per cent dextrose and normal saline in any proportions desired

The ketosis causes acidosis, i e, the diacetic and betahydroxybutyric acids are neutralized by the sodi um bicarbonate of the blood, leaving the blood poor in its alkali reserve The obvious remedy is to give sodium bicarbonate There are several objections to this procedure Large doses, up to 1 oz in 12 hours, have been proposed, but they often stimulate vomiting Soda given subcutaneously may cause a slough In travenous injections of soda solutions require sterili zation, and unless this is done with elaborate precau tions, the soda is converted to sodium carbonate, which is dangerous Furthermore, the use of large doses of soda in diabetics with ketosis tends to cause more extreme changes in the blood, producing alkalosis, than in normal individuals The dose is not easily controlled without the use of laboratory methods usually not available in private practice Fortunately the use of soda is seldom if ever a necessity The body will regenerate sodium bicarbonate as soon as it is able to oxidize the sugar and therefore the diacetic acid Also, the body has the ability to take the sodium from common salt as a source of sodium bicarbonate Normal saline is an excellent and perfectly safe substitute for soda Hartmann s Physiological Buffer Solution

intravenous use, the best U S P dextrose is the only kind allowable, and the solution must be sterile. The amounts of solution to be given should be such as compare in sugar content with the orange juice and sugar used above, i e, to inject 20 Gm sugar as a 5 per cent solution will require 400 c c

If pure dextrose is not available, recourse may be had to commercial corn syrup This is, of course, only for rectal administration To prepare the enema solution, use 5 oz Karo syrup (white or brown) and dilute it with warm water to make 1 qt. Add 2 tea spoonfuls of salt This is assumed to be equivalent to a 5 per cent solution of dextrose It should be warmed to the temperature of the body, 98 F, and from 2 to 4 oz injected slowly into the rectum with a rubber bulb syringe or any enema apparatus Some patients retain fluids better when given by the continuous drip method, others, when retention enemas are given at intervals of an hour Either method is, of course, to be preceded by the use of cleansing enemas, repeated until the fluid returned is really clear The amount of fecal material in the colon of comatose patients may be surprising Absorption is very poor if this cleansing is omitted

For the subcutaneous or intravenous administration of dextrose, the safest and most convenient way is to use the ampules of 50 per cent dextrose now marketed by a number of the drug manufacturers Every clinician and every hospital should have some such ampules always on hand This concentrated sugar solution may be injected intravenously to relieve se-

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guish the condition from an acute infection It is not uncommon to find patients who show all the common signs of a local inflammatory process in the abdomen such as acute appendicitis except that they are afebrile and it is true that untreated diabetics may have severe infections with little or no fever In such a case with recognized diabetic ketosis it is safest to assume that the condition is due to the diabetes alone The type of therapy (page 107) for coma has repeatedly been seen to give complete relief of the supposed inflammatory symptoms within 12 hours If the diabetes is brought under control and the abdominal situation is not relieved or if fever then manifests itself, there may be a complicating infection to be cared for Infections are of course, frequently the factors which precipitate coma Operations for suspected acute appendicitis or intestinal obstruction in diabetics should not be done unless the symptoms persist after the diabetic ketosis is brought under control, or unless fever develops

If even a slight fever is detected in a diabetic who is in coma or who is just recovering from severe acidosis the utmost pains should be taken to find the infection and to begin appropriate treatment at once In this acidotic condition the febrile response to infection is slight, therefore small elevations of temperature are the more significant

MAINTENANCE REGIME

When the comatose patient has been made "sugar-and acetone-free' the problem is the same as for the

(Lilly) is a safe and more effective substitute Furthermore, fruit juices are the normal source of soda for the body Therefore the methods already given, including the use of orange juice, sugar, insulin and saline, will furnish what the body needs and can best use

Accessory Factors in Treatment of Coma—The body is cold and should be made warm by the use of plenty of covers and of warm water bottles, there should be a minimum of exposure for examination and treatment. The pulse is always rapid in ketosis This is due to effects of the abnormal conditions on the blood and on the heart The blood has a reduced ability to carry oxygen and carbon dioxide, due to the acidosis The heart is weakened as are all the other muscles Blood pressure is low and pulse fast The remedies include the relief of acidosis, as above, and increased fluid to make up for that lost by diuresis due to the excretion of sugar and acetone bodies If blood pressure is alarmingly low, caffeine may be employed This is not often needed Restoration of a normal blood volume by supplying water is the fundamental method for relieving hypotension Certainly the heart does not require digitalis because of either fast rate or weak action The rate usually returns to normal in two or three days after acetone disappears from the urine Of course, if there is evidence of heart failure apart from the diabetic coma, there is no contra indication for the adminstration of digitalis

In coma, there is usually marked leukocytosis, with nothing about the differential blood picture to distin-

from glycosuria, i e, all the carbohydrate is being oxidized Once this condition has been met, further supply of calories may well be made by use of fats The diets listed in Table 2 on page 116 provide a simplified series covering the range of needs met with in clinical practice Maintenance diets for small children really imply diets which allow growth at normal rates These have never been found to be less than 1,500 calories except in cases of infants, for whom special feedings have to be used Maintenance diets for hard working adults have seldom been found necessary at a level higher than the 2,575 calories provided by the largest one in the list Increases of 220 calories between the smaller diets and of 305 calories between the larger ones of the series are provided by Diets 1 to 5 It is needless to provide for smaller differences than these These diets are planned according to the rule already mentioned It will be found that if a patient is free from glycosuria but shows acetone in the urine while using one of these diets, weight is not being maintained, i e, there is partial starvation The next larger diet may as well be used without further delay

These diets furnish more than the minimum protein which might be used safely in most cases The reason is that too low a protein intake makes a diet uninteresting and therefore leads the patient to eat food which is not allowed With this scheme, the totals of protein and fat are in round numbers, since the use of 1 or 2 Gm more or less of these materials is of little concern But it is important that the patient should be

patient who on first observation is not in danger of coma The physician must now plan a diet which will be adequate to keep the patient's body weight normal when he is occupied at his chosen work. Often the first diet tried will be too small It is better to start below the expected final level, so that the minimum diet will be used This is more economical of food and of insulin There is, however, no reason for keeping the diabetic below the optimum weight as given on pages 222 and 223 There is also no reason for interfering with the occupation of the diabetic The amount of physical exercise ought to be nearly uniform each day Otherwise there may be sugar in the urine on some days and insulin reactions on others (days of greater activity)

DIETS

There are many types of diet which are successfully used by specialists in this field Experience with the planning of menus for patients who desire not only tasty but economical diets has led to use of a series of diets based on relationships between fat and the total carbohydrate and protein used Although it is now known that these ratios have no validity in terms of fat oxidation the clinical fact remains that the use of high fat, low carbohydrate diets is successful It is unnecessary to go into the logic of the fat oxidation mechanism further than to assert that the first essential in a diet is to provide the minimum amount of carbohydrate which will prevent all ketosis This can be told only by trial, and when the urine is free

accurate about the measurement of his diet, in order to keep the food intake uniform and dependable and to discourage overstepping The instructions for the patients enable them to measure these foods with accuracy sufficient for clinical work, and they also allow of easy substitution which makes possible the variety in the diet that is necessary to insure coopera tion

Attention is called to the way in which milk has been incorporated in Diets 1A to 5A (pp 119-123) This is to meet the recognized needs of children for the protein, calcium phosphorus and vitamins which the milk will furnish Such diets are often welcomed by adults also They may be employed as occasional substitute menus to increase the variety in the diet

Reducing Weight of Diabetics—When the body weight is excessive as compared with the figures given on pages 222 and 223, it is important that the patient promptly lose the excess pounds That obesity may predispose to diabetes is commonly recognized The disadvantages of obesity to persons already diabetic include at least two factors in addition to those which make it undesirable to the nondiabetic The diabetes is more difficult to control in obese persons not only because their total heat production is relatively great which calls for excessive intake of food and use of insulin but also because uncontrolled fat storage probably causes the diabetes to progress Certainly the converse is true there is plenty of clinical evidence to show gains in carbohydrate tolerance in fat diabetics after they reduce The mechanism of this gain is not

TABLE 2

Comprehensive System of Diets and Diet Equivalents

			Normal Diets		Reducing Diets			Liquid Diet Equivalents			
									Milk or 5% Dextrose		
Diet No	Protein Gm	Carbohydrate Gm	Fat, Gm.	Calories	Diet No.	Fat Gm	Calories	Orange Juice Gm	Gm	Qt. and Oz.	
1	50	50	125	1 575	11	50	850	420	1 000	1	2
2	50	60	145	1,745	12	50	890	500	1 200	1	8
3	50	70	165	1 965	13	50	930	580	1 400	1½	
4	60	80	190	2 270	14	82	1 028	660	1 600	1½	6
5	70	90	215	2 575	15	60	1 180	750	1 800	1½	12
8	70	150	100	1 780				1 250	3 000	3	6

DIET No 1

Food	Portion, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.
Breakfast				
3% fruit	200			6
Egg (one)		6	6	
Bacon	15	2	8	
Bread	10	1		5
Butter	10		9	
20% cream	45	1	9	2
Total		10	32	13
Dinner				
Lean meat	70	18	11	
3% fruit and vegetable	400			12
Bread	10	1		5
Butter	20		17	
Mayonnaise	15		13	
20% cream	40	1	8	2
Total		20	49	19
Supper				
Lean meat	70	18	11	
3% fruit and vegetable	400			12
Bread	10	1		5
Butter	15		13	
Mayonnaise	15		13	
20% cream	35	1	7	1
Total		20	44	18
Total for Day		50	125	50

DIET No 1A

Food	Portion, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.
Breakfast				
Bacon	15	2	8	
Egg (one)		6	6	
Bread	10	1		5
Butter	15		13	
Milk	100	3	4	5
20% cream	75	2	15	3
Total		14	46	13
Dinner				
Lean meat	75	19	11	
3% fruit and vegetable	300			9
Butter	20		17	
Milk	100	3	4	5
20% cream	60	2	12	2
Total		24	44	16
Supper				
Egg (one)		6	6	
3% fruit and vegetable	300			9
Bread	10	1		5
Butter	15		13	
Milk	100	3	4	5
20% cream	60	2	12	2
Total		12	35	21
Total for Day		50	125	50

settled, but the need for losing the excess pounds is clear

To provide for loss of body weights, Diets 11 to 15 are offered The diet between nos 1 and 5 which will just maintain weight is first found, then the corresponding reducing diet is arrived at as follows The calculations are made so that carbohydrate and protein remain the same, but the fat allowance is materially reduced so that excess body fat is burned for energy in place of food fat It is found that if the patient is in proper equilibrium as to sugar, acetone and insulin when using such a diet as no 2, he can change to no 12 and vice versa without any disturbance in his sugar metabolism There is the same relationship between Diets 1 and 11, 3 and 13, etc. When the weight is reduced to the proper level, the patient is instructed to return to the original diet and its full allowance of fat These reducing diets allow rapid loss of weight, 2-4 lb per week, without any danger of weakness or infection If slower reduction is desired more fat can be included easily by the use of more butter, fatter cuts of meat or mayonnaise dressing

Low Fat Diets for Use with Gastric Disturbances — When for any reason a diabetic patient cannot be expected to use a complete or maintenance diet, it is of great importance that the carbohydrate intake shall not be reduced The fats are the most apt to disturb digestive processes, hence in any gastric upset they are reduced to a minimum The low fat diets used for reduction of weight are therefore also useful for

Diet No. 3

Food	Portion, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate Gm.
Breakfast				
3% fruit	300			9
Egg (one)		6	6	
Bacon	20	3	10	
Bread	20	2		11
Butter	20		17	
20% cream	40	1	8	2
Total		12	41	22
Dinner				
Lean meat	70	18	11	
3% fruit and vegetable	500			15
Bread	15	1		8
Butter	30		26	
Mayonnaise	25		21	
20% cream	35	1	7	1
Total		20	65	24
Supper				
Lean meat	65	16	10	
3% fruit and vegetable	500			15
Bread	15	1		8
Butter	25		21	
Mayonnaise	25		21	
20% cream	35	1	7	1
Total		18	59	24
Total for Day		50	165	70

Diet No 3A

Food	Portion, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate Gm.
Breakfast				
3% fruit	200			6
Bacon	20	3	10	
Bread	10	1		5
Butter	20		17	
Milk	60	2	2	3
20% cream	95	3	19	4
Total		9	48	18
Dinner				
Lean meat	85	21	13	
3% fruit and vegetable	400			12
Bread	10	1		5
Butter	30		26	
Milk	100	3	4	5
20% cream	95	3	19	4
Total		28	62	26
Supper				
Egg (one)		6	6	
3% fruit and vegetable	400			12
Bread	10	1		5
Butter	30		26	
Milk	100	3	4	5
20% cream	95	3	19	4
Total		13	55	26
Total for Day		50	165	70

Diet No. 2

Food	Portion, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.
Breakfast				
3% fruit	200			6
Egg (one)		6	6	
Bacon	15	2	8	
Bread	15	1		8
Butter	15		13	
20% cream	35	1	7	1
Total		10	34	15
Dinner				
Lean meat	70	18	11	
3% fruit and vegetabe	500			15
Bread	15	1		8
Butter	25		21	
Mayonnaise	20		17	
20% cream	35	1	7	1
Total		20	56	24
Supper				
Lean meat	70	18	11	
3% fruit and vegetable	400			12
Bread	15	1		8
Butter	25		21	
Mayonnaise	20		17	
20% cream	30	1	6	1
Total		20	55	21
Total for Day		50	145	60

Diet No 2A

Food	Portion, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.
Breakfast				
Bacon	25	4	13	
Egg (one)		6	6	
Bread	10	1		5
Butter	10		9	
Milk	60	2	2	3
20% cream	100	3	20	4
Total		16	50	12
Dinner				
Lean meat	70	18	11	
3% fruit and vegetable	300			9
Bread	15	1		8
Butter	30		26	
Milk	100	3	4	5
20% cream	35	1	7	1
Total		23	48	23
Supper				
Egg (one)		6	6	
3% fruit and vegetable	300			9
Bread	15	1		8
Butter	25		21	
Milk	100	3	4	5
20% cream	80	2	16	3
Total		12	47	25
Total for Day		51	145	60

Diet No. 5

Food	Portion, Gm.	Protein Gm.	Fat, Gm.	Carbohydrate Gm
Breakfast				
3% fruit	300			9
Eggs (two)		12	12	
Bacon	20	3	10	
Bread	15	1		8
Butter	15		13	
30% cream	60	2	18	2
Total		18	53	19
Dinner				
Lean meat	85	21	13	
3% fruit and vegetable	700			21
Bread	15	1		8
Butter	30		26	
Mayonnaise	25		21	
30% cream	60	2	18	2
Total		24	78	31
Supper				
Lean meat	80	20	12	
3% fruit and vegetable	700			21
Bread	15	1		8
Butter	30		26	
Mayonnaise	25		21	
Milk	170	5	7	9
30% cream	60	2	18	2
Total		28	84	40
Total for Day		70	215	90

Diet No. 5A

Food	Portion, Gm.	Protein Gm.	Fat, Gm.	Carbohydrate Gm
Breakfast				
3% fruit	300			9
Eggs (two)		12	12	
Bacon	20	3	10	
Bread	15	1		8
Butter	20		17	
Milk	100	3	4	5
30% cream	100	3	30	4
Total		22	73	26
Dinner				
Lean meat	70	18	11	
3% fruit and vegetable	500			15
Bread	15	1		8
Butter	30		26	
Milk	100	3	4	5
30% cream	100	3	30	4
Total		25	71	32
Supper				
Lean meat	65	16	10	
3% fruit and vegetable	500			15
Bread	15	1		8
Butter	30		26	
Milk	100	3	4	5
30% cream	100	3	30	4
Total		23	70	32
Total for Day		70	214	90

Diet No. 4

Food	Portion, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.
Breakfast				
3% fruit	300			9
Eggs (two)		12	12	
Bacon	20	3	10	
Bread	15	1		8
Butter	15		13	
30% cream	80	2	24	3
Total		18	59	20
Dinner				
Lean meat	70	18	11	
3% fruit and vegetable	700			21
Bread	15	1		8
Butter	20		17	
Mayonnaise	20		17	
30% cream	75	2	23	3
Total		21	68	32
Supper				
Lean meat	70	18	11	
3% fruit and vegetable	600			18
Bread	15	1		8
Butter	20		17	
Mayonnaise	20		17	
30% cream	60	2	18	2
Total		21	63	28
Total for Day		60	190	80

Diet No 4A

Food	Portion, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.
Breakfast				
3% fruit	300			9
Egg (one)		6	6	
Bacon	20	3	10	
Bread	10	1		5
Butter	20		17	
Milk	100	3	4	5
30% cream	100	3	30	4
Total		16	67	23
Dinner				
Lean meat	60	15	9	
3% fruit and vegetable	400			12
Bread	15	1		8
Butter	25		21	
Milk	100	3	4	5
30% cream	100	3	30	4
Total		22	64	29
Supper				
Lean meat	60	15	9	
3% fruit and vegetable	400			12
Bread	15	1		8
Butter	20		17	
Milk	100	3	4	5
30% cream	95	3	29	4
Total		22	59	29
Total for Day		60	190	81

TABLE 3—Liquid Diabetic Diets

Food	Total Daily Portion Diet No 11	Diet No 12	Diet No 13	Diet No 14	Diet No 15
Whole milk Gm	600	600	600	650	650
Skim milk, Gm				150	250
20% Cream Gm	40	40	40		
Cooked cereal Gm	50	50	50	100	100
3% vegetable puree Gm	60	60	60	60	100
Orange juice Gm	80	165	250	215	250
Eggs	3	3	3	4	4
Egg whites	2	2	2	2	3

Sample Menu of Liquid Diet in Three Meals

Breakfast	
Milk	100 Gm
Gruel made with	
Cooked cereal	50 Gm
Milk	50 Gm.
20% cream	40 Gm
Coffee	
Dinner	
Cream soup made with	
Tomato purée	60 Gm
Milk	100 Gm
Eggnog made with	
Eggs	2
Milk	150 Gm
Vanilla	¼ tsp
Milk	100 Gm
Supper	
Broth	200 Gm.
to which add	
Egg whites	2
Custard made with	
Egg	1
Milk	100 Gm
Vanilla	¼ tsp
Orange juice	80 Gm

Sample Menu of Liquid Diet in Six Meals

Breakfast	
Gruel made with	
Cooked cereal	50 Gm
Milk	50 Gm
Tea	
10 00 A. M	
Orange juice	80 Gm
Dinner	
Cream soup made with	
Tomato purée	60 Gm
Milk	100 Gm
Tea	
3 00 P M	
Eggnog made with	
Eggs	2
Milk	150 Gm
Vanilla	¼ tsp
Supper	
Broth	200 Gm
to which add	
Egg whites	2
Custard made with	
Egg	1
Milk	100 Gm.
Vanilla	¼ tsp
20% cream	40 Gm.
Coffee	
8 00 P M	
Milk	200 Gm.

such temporary conditions as these When a liquid diet is desired, as after tonsillectomy or after abdominal operations, it is most palatable if made up with a lower fat content than the usual diets for diabetics These same low fat diets serve this purpose It is simple to substitute in the menus given for these diets such materials as fruit juice, milk, eggs, thin cereals and soups to make low fat liquid diets Consequently, whenever a patient who is using Diet no 2 is to have a liquid feeding for one or more meals, the diet is changed to no 12 This alteration makes no changes in intake except in the fat Under these circumstances the body fat is used The amount of insulin required is not altered by such a shift The advantage of this plan is that changes may be made in either direction with no question as to the patient's tolerance for carbohydrate This tolerance remains unaltered unless infection anesthesia or operative shock causes a change Such a shift will not be followed by ketosis this is one of the most important parts of the postoperative treatment of diabetics

The readiness with which the liquid diet regimes can be arranged is illustrated in the suggested menus worked out in Table 3

Table 3 gives the amounts of several liquid foods which may be used with convenience to make up liquid diets of the low fat type The amounts given in any column under a diet number are the total amounts of that food to be used in the 24 hours of one day It is expected that the milk and eggs or egg whites may be combined to make eggnogs Or the pureed

DIET No 13

Food	Portion, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.
Breakfast				
3% fruit	300			9
Egg (one)		6	6	
Bread	15	1		8
Butter	5		4	
20% cream	40	1	8	2
Total		8	18	19
Dinner				
Lean meat	80	20	12	
37 fruit and vegetable	600			18
Bread	15	1		8
Butter	5		4	
Total		21	16	26
Supper				
Lean meat	80	20	12	
37 fruit and vegetable	600			18
Bread	15	1		8
Butter	5		4	
Total		21	16	26
Total for Day		50	50	71

DIET No 14

Food	Portion, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.
Breakfast				
3% fruit	300			9
Egg (one)		6	6	
Bread	15	1		8
Butter	5		4	
20% cream	20	1	4	1
Total		8	14	18
Dinner				
Lean meat	100	25	15	
3% fruit and vegetable	800			24
Bread	15	1		8
Butter	5		4	
Total		26	19	32
Supper				
Lean meat	100	25	15	
3% fruit and vegetable	700			21
Bread	15	1		8
Butter	5		4	
Total		26	19	29
Total for Day		60	52	79

Diet No 11

Food	Portion Gm.	Protein Gm.	Fat, Gm.	Carbohydrate Gm.
Breakfast				
3% fruit	200			6
Egg (one)		6	6	
Bread	10	1		5
Butter	5		4	
20% cream	40	1	8	2
Total		8	18	13
Dinner				
Lean meat	80	20	12	
3% fruit and vegetable	500			15
Bread	10	1		5
Butter	5		4	
Total		21	16	20
Supper				
Lean meat	80	20	12	
3% fruit and vegetable	400			12
Bread	10	1		5
Butter	5		4	
Total		21	16	17
Total for Day		50	50	50

Diet No. 12

Breakfast				
3% fruit	200			6
Egg (one)		6	6	
Bread	15	1		8
Butter	5		4	
20% cream	40	1	8	2
Total		8	18	16
Dinner				
Lean meat	80	20	12	
3% fruit and vegetable	500			15
Bread	15	1		8
Butter	5		4	
Total		21	16	23
Supper				
Lean meat	80	20	12	
3% fruit and vegetable	435			13
Bread	15	1		8
Butter	5		4	
Total		21	16	21
Total for Day		50	50	60

These liquid diets are for use during emergencies only Such occasions are after removal of several teeth removal of tonsils stomach disturbances or when recovering from operations or fevers It is *often advisable to divide these liquid diets into more* than three feedings The number of times food is given in the day may be varied as much as seems desirable When using insulin, the food ought to be given at least every eight hours and each feeding should contain either some of the milk or some of the fruit juice

Postoperative Diets —When the feeding must be limited to orange juice, the appropriate amount for 24 hours is to be found in Table 2 (p 116) in the column near the right side For any given diet the amount of orange juice prescribed will furnish the same carbohydrate as the diet on the same horizontal line If milk is desired as the only food the amount is larger than for orange juice, since milk contains 5 per cent of sugar as compared to the 12 per cent sugar in orange juice Often it is convenient to use half the milk allowance and half the orange juice allowance These 24 hour totals may be divided up into any number of feedings

If feeding by mouth is not allowable, 5 per cent dextrose solution may be given by rectum subcutaneously or intravenously, just as described for the treatment of coma The amount to be used is the same as the amount of milk given in the table The best way to do this for postoperative cases is to plan the total fluid intake for 24 hours so that it will include this

Diet No. 15

Food	Portion, Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.
Breakfast				
3% fruit	400			12
Eggs (two)		12	12	
Bread	15	1		8
Butter	5		4	
20% cream	30	1	6	1
Total		14	22	21
Dinner				
Lean meat	100	25	15	
3% fruit and vegetable	800			24
Bread	15	1		8
Butter	5		4	
Total		26	19	32
Supper				
Lean meat	100	25	15	
3% fruit and vegetable	800			24
Bread	15	1		8
Butter	5		4	
Skimmed milk	100	3		5
Total		29	19	37
Total for Day		69	60	90

vegetables may be cooked with milk to make soups The egg whites and the orange juice may be whipped together to make an albuminized drink Egg white may be added to hot broth, pouring the egg in slowly and beating constantly until the egg coagulates The cereals are to be cooked as usual, 1 part of dry cereal in 4 parts of water, and then they are to be thinned with warm milk to make liquid gruels Cream is used with coffee, since it is understood that in addition to the foods listed here coffee, tea or clear broth may be used If desired, the whole egg may be used instead of the egg whites mentioned, since this adds only a little fat Or if the egg yolk is not well taken all the eggs may be used without the yolks

Less than this has never been found to maintain a patient This diet is, however, sufficient for children and for many inactive or small adults As soon as it becomes evident that this diet is inadequate to satisfy the needs of the patient, a shift may be made to some higher diet The extent of the addition called for depends upon the activity of the patient It is easier to make small additions several times than to make large additions and then to have to retrace The determination as to the final diet on which a patient is to be maintained is made by the ability to control the body weight while the patient is engaged in the activity customary for him Children or emaciated adults should be able to gain weight

If the patient has been treated with insulin to relieve coma or to prevent the threatened onset of this complication, it is well to continue using insulin without interruption when establishing the dietary level Adjustment of insulin dosage is made by small changes until there is no glycosuria and no evidence of insulin reaction

If the patient did not have acetone bodies in the urine at the beginning of the treatment, insulin need not to be used at once After trying Diet no 1 for four days the urine will usually be found to be free from sugar in such cases If there are still significant amounts of sugar in the urine at this stage of treatment, the situation is usually complicated by such factors as dishonesty or inaccuracy of the patient in food limitation or by the presence of fever, thyrotoxicosis gangrene or acetone in the urine In such cases

amount of 5 per cent dextrose solution Allow at least four hours for enemas, rest and time when the patient will not be receiving the fluids The 24 hour total is then divided equally among the 20 or less hours, and the fluid given at a uniform rate by rectal drip or other injection method If insulin is to be used with such feedings, it can be given in equal doses at six or eight hour intervals If the injections are made intravenously or subcutaneously, the insulin may be added to the proportionate part of the fluid Rectal administration of insulin is futile

Choice of Diet—When diagnosis of diabetes is made but there is no acetone in the urine and there are no evidences of an emergency, a scheme of moderate restriction is almost always desirable Under such conditions it is safe to advise the patient to omit all sugar, all bread, all other foods prepared with flour and all potatoes, after four days of which routine he may again be examined If sugar has disappeared entirely from the urine, additions to the diet may be made at intervals of two or three days as long as no glycosuria appears at any time of day The urine should be tested two hours after each meal In this way, a qualitatively restricted diet may be found satisfactory If the urine is not made free from sugar within the first four days by this simple plan, the only safe and dependable scheme is to go at once to a carefully measured diet program Most diabetics need to be required to measure their diets as the surest way of enforcing cooperation with the physician

Usually it is well to begin with the use of Diet no 1

tations of this vascular disease complicate the treatment of diabetes See page 153 for mention of these complicating factors

2 Carbohydrate for Work Experience with patients using these diets which furnish large amounts of fat with small amounts of carbohydrate shows that they can do muscular and mental work with their normal strength and speed if their diets are ample to keep up the body weight and if their urine is free from sugar With sudden demands for unusual amounts of work, it is necessary to give additional food but this may as well be a combination of 2 parts of fat to 1 of carbohydrate Since it is difficult to give exactly the amount of food that is needed for a specified piece of work, these adjustments are difficult to make This is the reason for recommending that the diabetic have approximately the same amount of physical exercise each day

3 Dishonesty in Food Measurement There is no known scheme for treating diabetics which does not frequently lead to infractions of the restrictive rules The human desire to be free from imposed limitations and the natural appetites are adequate explanation for this There is no need to suppose that diabetics are by the nature of their disease dishonest The fact is that when a patient with average intelligence has his condition explained to him he can be persuaded to cooperate in a plan for the management of the condition without the use of external force The problem is then to secure a program which will most nearly satisfy the appetite the physiologic needs and the

after the measurement of food has been found to be accurate time can be saved by prompt use of small doses of insulin Often such patients will make enough progress to be able to dispense with the use of insulin after a few weeks

The only satisfactory way to arrive at a permanent diet level for a given diabetic patient is to continue to increase the diet until weight is maintained, using insulin in sufficient quantities to keep the urine free from sugar throughout the day The diets as given in this scheme, from no 1 to no 5, are planned so as to use the maximum amounts of fat and the minimum of carbohydrate that can be depended upon Criticism of such a high fat diet regimen has been made on the following grounds (1) that they tend to produce arteriosclerosis (2) that they do not furnish sufficient carbohydrate for efficient work, (3) that they lead to dishonesty in food measurement, (4) that they are expensive, (5) that they do not satisfy

These criticisms may be met satisfactorily in the following ways

1 Arteriosclerosis Arteriosclerosis is a common cause of diabetes There is some suspicion that diabetes causes sclerosis but this is far from being proved There are now known to be many diabetics who have lived for periods up to 20 years on the high fat diets without evident development of arteriosclerosis This certainly casts doubt on either diabetes or high fat diets as causes of arteriosclerosis The sclerotic process sometimes begins very early in life, for reasons still unknown The many manifes

from the 9 per cent group, one-fourth as much from the 12 per cent group, one fifth as much from the 15 per cent group or one sixth as much from the 18 per cent group Since fruits and vegetables are classified together in the diet plan, in order to have both fruit and vegetable at a given meal a certain portion must first be reserved for fruit, then the remainder taken as vegetables Thus, if the allowance were 500 Gm of 3 per cent fruit or vegetable 200 Gm might be used as fruit and the remaining 300 Gm as vegetable The protein content of all the vegetables and fruits is assumed to be 1 per cent The small variations from this amount of protein which occur are not important unless large amounts of a certain few vegetables are used frequently These vegetables which contain more protein are beans corn peas and potatoes

Higher Carbohydrate Diets —If it becomes apparent that despite the firm insistence of the physician the patient refuses to cooperate on such a program as that prescribed compromise is better than failure to keep some sort of adequate treatment under way The goals of therapy are the maintenance of body weight and strength and the conservation of health so that diabetes alone shall be no more than a nuisance, certainly not a handicap The scheme mentioned is the most economical financially and physiologically If the patient chooses to use more carbohydrate with less fat, he may safely do so There are two conditions to be insisted upon uniform dietary intake and continuous freedom from glycosuria It is emphatically impossible to care for a diabetic satisfactorily if the

financial abilities of the patient. There is no longer room for serious doubt that the high fat type of diet can properly furnish what the body needs

4 Least Expensive Diets The cost of special diets is unfortunately always a bit higher than the average diet in this country Such diets are not much higher than the best diets which are now recommended for the use of well people The expensive items are fruits and vegetables, as compared with bread and potatoes The high fat type of diet may cost from 5 to 10 per cent more than a lower fat diet Furthermore the cost of a higher carbohydrate allowance must include the increased amount of insulin which is made necessary These factors lead to the choice of the high fat diets as the most economical among adequate diets for diabetics

5 Satisfying the Appetite The menus should be planned so that patients are given sufficient bulk to satisfy the desire for a full stomach and to act as a mechanical stimulant to peristalsis The bulk is best supplied by the vegetables and fruits When bulk is excessive, use is made of the more concentrated foods, i e, the 12-18 per cent fruits and vegetables rather than the 3 per cent group The standard menus supplied are all written in terms of the 3 per cent vegetables and fruits, since these are most commonly desired This does not mean that those fruits and vegetables in the higher percentage groups cannot be used For variety, the amount of 3 per cent fruit and vegetable allowed in the diet may be replaced by half as much from the 6 per cent group one third as much

betics who must depend upon such a source of food, it is unsafe to plan on less than about 100 Gm carbohydrate per day This may necessitate the use of insulin where it would otherwise be unnecessary but by such a plan a man may be allowed to continue his occupation

DIET No 8

Food	Portion, Gm	Protein, Gm	Fat, Gm.	Carbohydrate Gm.
Breakfast				
3% fruit	500			15
Cooked cereal	100	3		12
Bacon	20	3	10	
Bread	30	3		16
Butter	10		9	
20% cream	75	2	15	3
Total		11	34	46
Dinner				
Lean meat	90	23	14	
3% fruit and vegetable	1 000			30
Bread	30	3		16
Butter	15		13	
20% cream	40	1	8	2
Total		27	35	48
Supper				
Lean meat	90	23	14	
3% fruit and vegetable	1 000			30
Bread	30	3		16
Butter	10		9	
Mayonnaise	15		13	
Milk	200	6	8	10
Total		32	31	56
Total for Day		70	100	150

DIET 8B—WITH 120 GM FAT Add 20 Gm butter or mayonnaise to diet 8.

DIET 8C—WITH 140 GM FAT Add 35 Gm. butter or mayonnaise and 45 Gm 20% cream to diet 8

DIET 8D—WITH 160 GM. FAT Add 60 Gm. butter or mayonnaise and 45 Gm 20% cream to diet 8

DIET 8E—WITH 180 GM FAT Add 75 Gm. butter or mayonnaise and 75 Gm 20% cream to diet 8.

DIET 8F—WITH 200 GM FAT Add 80 Gm butter or mayonnaise 155 Gm. 20% cream and 10 Gm bacon to diet 8

diet is not planned so that the daily food intake is constant, especially in its carbohydrate content This is why weighing of the food is so important The patient who uses insulin finds this more important than does the patient with milder diabetes The severe diabetic must keep himself in the rather narrow zone between hypoglycemic reactions from too little food and hyperglycemic loss of tolerance from food excess This is usually simpler than it sounds, if only the patient is trained from the beginning to be accurate in food measurement.

For patients who are to have relatively high carbohydrate and lower fat diets, a typical menu is provided under no 8 (p 137) This serves as a definite diet, furnishing 1,780 calories, for use in very mild cases or for patients who are to use higher carbohydrate allowances with the consent of the physician Obviously this menu can be altered by the addition of fats to secure such calorie levels as are desired For this purpose a series of supplements, B to F, will add 20-100 Gm fat, and thus 180 900 calories as needed This type of diet, with relatively high carbohydrate, is made almost necessary for those occasional patients who must get their meals at restaurants in different places as they travel about The reason for this condition is that most public eating places not only plan their meals with bread potatoes and baked cereal products as the chief items but also omit from the foods available a sufficient variety of fruits and vegetables to allow a satisfying meal to be secured with a moderate amount of carbohydrate For dia

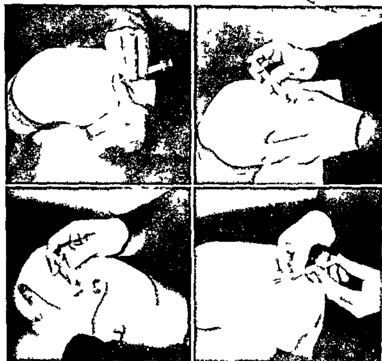
It is sufficient that these urine samples be reported whether in the hospital or at home, as 'sugar-free showing a "trace' or a large amount of sugar By sugar-free, it is meant that the Benedict test remains clear blue After boiling the tube with the Benedict's reagent and urine mixture, shake it well just before examination Transparent green color or occasional gray flakes of precipitate do not indicate sugar A yellow precipitate which mixes with the blue Benedict solution on shaking causing the whole to appear *green* indicates a "trace' of sugar Precipitate sufficient to obscure the blue color and render the whole solution *yellow* red or brown, is reported as showing a 'large amount' of sugar There is not much reason to attempt further differentiation Changes in the rate of water excretion may affect the variations in concentration of sugar in the urine without any significance as to change in the metabolic fault which is the problem in diabetes The objective to be held clearly in mind is complete and continuous freedom from sugar in the urine

THE USE OF INSULIN

Insulin is made by four firms in the United States Burroughs Wellcome & Co Eli Lilly and Company E R Squibb & Sons and Sharp & Dohme The product of all the manufacturers is carefully tested by them and also by the Connaught Laboratory at Toronto where insulin was first prepared We are therefore assured that insulin from one manufacturer is just as

URINE TESTING

There is little need for determining the amount of sugar in the urine It is entirely unnecessary that a patient should know how to titrate the sugar by the quantitative methods Also, there are not many occasions when it is of value to have the 24 hour urine samples examined for sugar But it is of great value in arranging the diet and the insulin dosage for a given patient to know at what hours of the day sugar is lost and whether these losses are mere traces or significant amounts During hospital study, it is well to have all urine saved in several containers and the separate fractions of the 24 hour specimen tested for sugar The best hours for division of the daily specimen are essentially (1) 7 00-9 00 a m , (2) 9 00-12 00 (3) 12 00-3 00 p m , (4) 3 00-6 00, (5) 6 00-9 00, (6) 9 00 p m to 7 00 a m Specimens 1, 3 and 5 show the immediate results of meals In cases which show sugar in these specimens only, it may be sufficient to change the menu so that less concentrated forms of carbohydrate are taken Sometimes shifting bread or fruit from one meal to another will settle the question of how to stop a slight glycosuria discovered by this fractional test These separate tests will guide the physician in altering the doses of insulin to stop all glycosuria without producing frequent insulin reactions By the liberal use of these urine tests it is possible to conduct cases of diabetes satisfactorily without any blood sugar tests after the initial diagnostic blood sugar determination has been made



TECHNIC OF INSULIN INJECTION

Fig 20 (upper left) —Thumb is drawing skin toward body so that needle may pass through stretched portion toward knee

Fig 21 (upper right) —Thumb and finger are drawing skin tight between them for needle to pass through

Fig 2? (lower left) —Thumb is drawing skin toward knee and needle pointed toward body

Fig 23 (lower right) —After inserting the needle to position shown in Figure 20 the insulin is ready to be injected

strong as that from any other There are no demonstrated advantages of one brand over the other It is perfectly safe to change from one brand to the other if the same concentration is used Fortunately, all the manufacturers have agreed to use the same colored labels, yellow for U-20, red for U-40 and green for U-80

Insulin can be purchased in at least three different concentrations These are designated as U-20, U-40 and U-80, which symbols mean that 1 c.c contains 20, 40 or 80 'units' of insulin The "unit' is a definite amount and it does not vary, even though it be taken from bottles of different concentration It is usually not good practice for the patient to change from one concentration of insulin to another, for he may make a mistake in the measurement The chief advantage of the more concentrated forms is that when large doses must be given, they can be injected without having to inject large amounts of water The more concentrated solutions are somewhat cheaper than the dilute ones, therefore, patients wish to use the most concentrated form However there is some unavoidable waste in the removal of insulin from the vials etc The loss of insulin is proportionately greater with the more concentrated solutions It is not necessarily good economy to buy the form of insulin which costs least per unit The general rule for deciding which strength to use may be stated as follows use that form of insulin which will make the injection not less than 0 2 c c or more than 1 c c

The patient can easily be taught the proper technic

for the administration of insulin (Figs 20 23)

Adjustment of Insulin Dosage —It must be remembered that some 20 minutes are necessary from the time urine is formed in the kidney until it can be voided Ordinarily, urine collects in the bladder for periods up to eight hours before it is passed Therefore the urine obtained at any given time contains sugar if at any time since the last voiding the blood sugar has been high enough to cause glycosuria Under the influence of insulin the blood sugar may well change from such a level as 250 mg at 7 00 a m to 50 mg at 9 00 a m Urine accumulated in the bladder during this two hour interval will contain some sugar owing to the high blood sugar level at the beginning This will serve to explain what has often puzzled physicians, viz, the finding of glycosuria when urine was tested during the symptoms of insulin reactions When confronted by such a situation, sugar should always be administered to relieve the reaction The prevention of such reactions is accomplished by reducing the insulin dose given just before the time a reaction usually occurs It may be necessary to raise the last preceding dose so as to keep the blood sugar from rising to an abnormally high level In other words early morning glycosuria often calls for a larger dose of insulin at supper time or for use of the evening insulin shortly after supper or occasionally for an extra small dose of insulin late in the evening

Solution of Zinc Insulin Crystals —The more recently developed crystalline form of insulin made with

specimens taken at about 2 00 and 5 00 p m These will show the direction of change The study of fractional urine specimens is as useful as with standard insulin The aim of therapy is still to maintain the patient without glycosuria If this appears too difficult it is usually possible to allow only traces of glycosuria and always to prevent the excretion of any acetone Less than this cannot be considered adequate control of diabetes

Protamine zinc insulin acts more slowly than the standard form and is therefore not to be relied on when the presence of coma necessitates action without delay Combined use of protamine zinc and standard insulin may be helpful at such times No directions for such procedure can yet be based on sufficient experience to allow definite statements But in cases where a uniform dose of protamine zinc insulin has been found successful and intercurrent disease or other disturbance makes an increased dose temporarily necessary, it is possible to add standard insulin if prompt change is desired More commonly, the dose of protamine zinc insulin is increased, and later reduced when reactions and freedom from glycosuria indicate that the change may be made In the case of protamine zinc insulin, the action of a given dose lasts for more than 24 hours Therefore daily doses have a cumulative action and the effectiveness of any dosage cannot be estimated until it has been used for about four consecutive days Changes of dosage are usually not made until time has allowed such observation

the addition of small amounts of zinc, is now sold under the term "solution of zinc insulin crystals" When first introduced it was thought to have more prolonged action than the older, or "standard" insulin The difference is so slight that these two forms may be used interchangeably Probably the older type will disappear from the market, since the crystalline form is now widely used and has the advantage of less frequent allergic reactions

Protamine Zinc Insulin —Protamine zinc insulin is a preparation of a precipitated insulin which dissolves slowly at the reaction of subcutaneous fluids thereby making its activity felt more slowly but for many more hours than with standard insulin This leads to greater efficiency per unit and consequently lower dosage, averaging a saving of about one fourth of the daily dose Owing to slow action, the total daily dose may usually be given in a single injection in the morning Since the first effects are not recognized for a few hours, it is a matter of no concern whether this injection be before or after breakfast Morning routine dosage seems most advantageous Protamine zinc insulin is less stable than the standard form and carries an expiration date It should be kept refrigerated but not allowed to freeze

The blood sugar level of patients using protamine zinc insulin will often be found to drop progressively during the afternoon and evening and the occurrence of insulin reactions therefore may be at any hour of the day or night In judging the adequacy of dosage the morning blood sugar is often not so helpful as two

in the rates of absorption and, therefore, inconstant control of diabetes Recently the two types of insulin have been mixed in the vial in order to secure uniformity Owing to the fact that there is in commercial protamine zinc insulin an excess of protamine a considerable quantity of crystalline insulin must be added before any change in character of the mixture can be shown Clinical trials of different proportions and of mixtures stabilized at different acidities are now under way but it may be some time before any such mixture is made available by the manufacturers If a clinician desires to use such mixtures he should instruct the patient in meticulous detail about the preparation of the mixed insulin and should follow the suggestions of one or another of the clinical workers who recommend effective mixtures, until commercial and stable preparations become available

Another approach to this same problem is the use of other types of protein than protamine in the combination with insulin In the United States the only one of commercial importance is globin zinc insulin The delay in securing initial action is greater than with crystalline but less than with protamine insulin The duration of activity of a single dose is less than 24 hours Therefore nocturnal hypoglycemic reactions are rare On the other hand the time characteristics of globin insulin lead to hypoglycemia in the afternoon and often diabetics who use this type of insulin must interrupt the afternoon program for an extra lunch Also the exhaustion of activity in less than 24 hours makes this form of insulin poorly adapted for treat

When protamine zinc insulin is to be substituted for standard insulin the following simple scheme will often allow the change with no trouble, little glycosuria and seldom any risk of serious amounts of acetone excretion Give the morning dose of standard insulin as usual At noon, administer one-half the total daily dose in the form of protamine zinc insulin No insulin is given in the evening The next morning and thereafter, omit the standard insulin and give three fourths of the previous daily dose as one injection of the protamine zinc insulin Then adjust the doses as indicated by urine and blood tests

Protamine zinc insulin is available in U-40 and U 80 concentrations, with red and green labels, respectively Since it is now possible for many patients with severe diabetes to use from 40 to as much as 100 units at a single daily injection, the advantage of the U-80 concentration will be apparent Syringes are calibrated with a scale for 40 units on one side, for 80 units on the opposite

To circumvent the difficulties of using large doses of protamine zinc insulin, two procedures are in use If the dose is large it may produce a hypoglycemic reaction during the night if reduced to avoid this, it may permit glycosuria immediately after meals, especially in the morning The most obvious way around the handicap is to administer part of the insulin as crystalline zinc insulin This would require two separate injections, adding to the details and nuisance of therapy Attempts to combine the two types of insulin in the syringe are followed by some variability

ance for sugar, thus allowing a lower dose of insulin

Allergy to Insulin—For those occasional diabetics who have an allergic sensitivity to the usual commercial form of insulin, the manufacturers have prepared several special types of insulin from different species More recently the introduction of solutions of zinc insulin crystals has offered a more highly purified form of the hormone with much less tendency to arouse allergic responses Even this form is not without occasional local reactions suggesting allergy With rare exceptions those patients who manifest allergic sensitivity to insulin overcome that difficulty after a few days or weeks of routine use

INFECTIONS OCCURRING IN DIABETICS

Infections of any sort should be treated as carefully and as promptly as possible In addition to the ordinary medical and surgical problems to be met, there are additional factors affecting food and insulin requirements First, the carbohydrate intake should never be reduced from the usual level if the patient is using insulin If there is much fever the total calories required are increased and partial starvation will occur if the diet is not increased, although inactivity with bed rest tends to offset this factor Except with high fevers the diet in use is adequate If the food must be given in soft or liquid form, see the directions given in Table 3 on page 125

With almost any infection there is loss of the body's ability to use sugar, and in diabetics this shows as a

ment of severe diabetes with one daily dose As a consequence, a number of students of clinical diabetes question the permanent importance of globin zinc insulin It is hoped that a still better form of delayed action insulin may be produced

Objections Raised against Insulin —Insulin is never "habit-forming" Of course, most diabetics who need insulin at one time continue to need it This is no more a habit-forming drug than is food habit-forming because if we once begin to eat we must continue to do so The dose of insulin is often reduced as tolerance increases during adequate treatment. Some patients have to have increasing doses as the disease becomes more severe This is almost always due to negligence or infection

There is as yet no substitute for insulin that has given any satisfaction for sustained use Many substitutes are offered Their trial outside a hospital organized for experimental work is still extremely hazardous

Insulin shocks are unpleasant, and occasionally they may prove dangerous They are to be avoided *But* to refuse to prescribe insulin because of the danger of reactions is just as plausible as to refuse to treat a patient with severe diphtheria with antitoxin because of the occasional case of serum sickness In both cases the medical man must learn how to avoid the unnecessary reactions when possible and how to treat them when they occur Patients should be told that insulin reactions are likely to occur but that they should usually be welcomed as indicators of returning toler-

is superficial and healing may take place with no surgical treatment These dry areas should be protected from injury and should not be subject to maceration Warmth and other measures to improve the circulation are the only treatment *Avoid direct or excessive heat to sclerotic diabetics* because their skins are insensitive and therefore they may be burned before they give warning of excessive heat A burn is essentially a new gangrenous ulcer For detailed information about surgical work on diabetic patients, consult *Diabetic Surgery* by L S McKittrick and H F Root[2]

Chemical Amputation of Gangrenous Small Parts —Trial of a new method of amputation of gangrenous toes or small areas on other parts of the feet has been made over several years past with gratifying success Mohs[3] has applied specially designed pastes containing zinc chloride to small parts which are to be removed This fixes the tissue in situ without proximal necrotizing action The pain is limited to a few hours controllable with opiates After a few days the fixed tissue can be dissected off without local anesthetic or hemostasis Healing by granulation and epithelization is usually satisfactory The technic requires meticulous personal attention but is recommended in many cases in which ordinary conservative surgical procedures seem contraindicated and radical amputations are being considered

Controlled Heat for Foot Lesions —Obviously the

2 Ph'l d lph Le & F b ger 1928

3 F E Mohs E L Sev inghaus d E R Schmidt. Conservati Ampu tion of G grenou P rts by Ch mos gery An S rg 114 274-282 A gust 1941

further loss of sugar tolerance In addition, there is seen in some cases an inhibitory action of toxins on insulin Consequently, infections are prone to make increased insulin dosage necessary Sometimes a patient with mild diabetes is made temporarily so ill that he must have insulin during an infection, although diet limitation alone is otherwise sufficient. These results of infection are almost always temporary, but the use of insulin in doses adequate to control the diabetes is important for prompt recovery

The same factors mentioned also suggest that infections of the teeth sinuses, tonsils, gallbladder, appendix etc, should be given attention to reduce severity of diabetes and for general health

GANGRENE OCCURRING IN DIABETICS

There is no reason for considering the gangrene that is seen in diabetics as different in etiology from that seen in other arteriosclerotic patients The presence of gangrenous tissue often makes diabetes more difficult to treat, in much the same way that infections affect diabetes Also, if the gangrenous tissue occurs in a diabetic organism secondary infection seems a bit more common The treatment is, however along the accepted lines of surgery which usually means amputation at a level high enough to get a sound stump with good circulation The medical management is essentially the same as that outlined for infections In cases with dry gangrene limited to a small area, such as a toe or a spot an inch or less in diameter the lesion

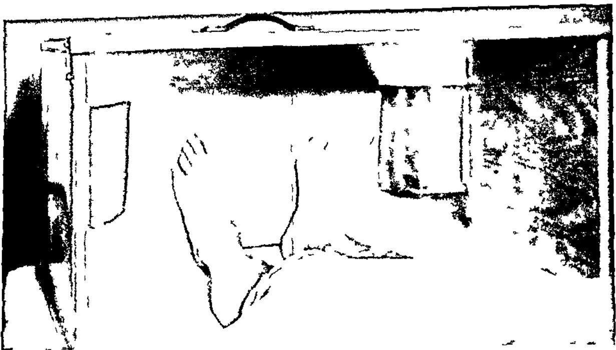


Fig 24—*Amacker heat control chamber* 30 in wide 16 in high 23 in deep Forty watt bulbs behind the two baffle plates supply heat Thermometer and thermoregulator behind screen panel maintain temperature within 2 F

healing of lesions on the feet and calves would be faster and more certain if the temperature of these parts could be maintained near that of the face and trunk The usual devices, such as the hot water bottle, electric pad or bed cradle with a simple electric light bulb have disadvantages and some dangers Excessive heat causes vasoconstriction and defeats the purpose of moderate warmth which will improve the circulation To meet this situation, a warm chamber has been devised It provides automatically controlled temperature, with electric lights as sources of heat The chamber is so constructed that the feet cannot be burned or injured Not only is there no discomfort or inconvenience attached to the use of this chamber on the bed, but it adds genuine increase in comfort to those sclerotic individuals who have impaired circulation in the legs Such chambers and directions for their use can be purchased directly from the manufacturer Mr John R Amacker, Stanley, Wis (See Figure 24)

EXERCISES FOR ARTERIOSCLEROTIC PATIENTS

The most successful means of improving the circulation in the legs and feet of these older patients is the use of Buerger's exercises It is not known how they accomplish results Relief from the aching pains the cramps and the coldness is usually reported as coming in two to four weeks after beginning the exercises It is a safe scheme for any patient to use for an indefinite period of time The only equipment is a board or

a few pillows to support the leg so that the foot is about 2 ft higher than the hip While the patient is lying on the bed he elevates the leg and foot until the leg is blanched, requiring two to four minutes Then the leg is allowed to hang over the side of the bed until it is congested, requiring a similar time If this causes the leg to ache in less time, he should proceed to the third step resting the leg horizontally on the bed for three or four minutes During rest, it is helpful to use the carefully controlled electric warm chamber to get the leg warm *Avoid any possibility of burns* Repeat this routine for an hour, three times daily

SYMPTOMS ASSOCIATED WITH DIABETES

General

Obesity — Always due to eating more than is necessary Obesity makes diabetes worse It frequently precedes discovery of glycosuria (See p 117)

Emaciation — Loss of weight is seen with severe diabetes when proper treatment has not been used Loss of weight after the urine is sugar-free indicates inadequate diet

Fever — Seen only with infections Slight fever is especially significant in comatose diabetics

noids, etc, tends to make diabetes worse Focal infection should be thoroughly removed if possible There is also a marked tendency for diabetics to become easily infected Healing may be better when diabetes is under control This should be ap parent in a few weeks

CIRCULATORY SYSTEM

Murmurs

Soft nontransmitted systolic murmurs are common sometimes transi tory and are not indicative of valvu lar lesions

Hypertension Arteriosclerosis

There is frequent arterial disease and hypertension in diabetics Arteriosclerosis is a common cause of dia betes The reverse is probably not true

Hypotension Dyspnea Edema

These evidences of slight myocar dial inadequacy do not necessarily require specific cardiac medication, such as digitalization The improved power of the myocardium after dia betes is controlled often gives relief from these symptoms

Flushed Skin Tachycardia Kussmaul Respiration

These are evidences of acidosis approaching coma (See p 107 for the treatment) No digitalis is needed Keep patients in bed until tachycardia is relieved

Weakness
Fatigue
Slow Mental Responses
Amenorrhea
Impotence

These are evidences of the general depression of many bodily functions observed in severe diabetics They are usually completely relieved when adequate treatment of diabetes has been provided If not relieved further causes should be sought

EYES

Blurring
Diplopia
Scotomas
Fatigue

These are manifestations of the disturbance due to diabetes, and they may be expected to disappear after the patient has been kept without glycosuria for a few weeks Refraction should never be done for the fitting of spectacles until the patient is free from sugar for at least one month

Soft Eyeball

This is seen in marked acidosis, a diagnostic help in coma There is rapid return to normal tension when the acidosis is relieved

Cataracts

These are seldom due to diabetes Generally treatment should be as for senile types in nondiabetic patients

MOUTH AND THROAT

Teeth
Tonsils
Adenoids

Cavities, pyorrhea and infected roots are often due to the use of diets without enough vegetables and fruits Any infection in teeth tonsils ade

Edema

When edema occurs after beginning treatment for acidosis, it may be ignored, since it is temporary and will clear spontaneously in not more than two weeks

Skin

Furuncles Carbuncles

Caused by poor resistance to infection often in part by lack of cleanliness Treat as for nondiabetics and also treat the diabetes

Pruritus Pudendi

Caused by the fermentation of sugar in the urine which is allowed to dry on the skin Scrupulous cleanliness plus skin lubrication will relieve and prevent it Try cold cream or use lycopodium as a dusting powder

Laboratory Findings

Glycosuria

Assume diabetes when sugar is found unless morning blood sugar is normal

Ketonuria

Acetone and diacetic acid mean starvation If there is also sugar in the urine insulin is needed (See pp 103 and 107)

Albuminuria Casts

These are evidences of acute damage to the kidney during acidosis Renal function will return to normal

Abdomen

Constipation	Common, due to muscular atony Use exercise, vegetables, bran wafers, mineral oil and salines, in the order given
Pain	Abdominal pain usually in the region of the appendix, is seen in many cases of acidosis approaching coma (See p 113 before operating)

Legs

Cramps	Usually in the calf muscles Relieved by treating the diabetes
Reflexes	Usually reduced or absent patellar reflexes May return in young patients
Pain *Anesthesia* *Paresthesia*	These are manifestations of the reduced circulation in the legs and of the degenerative lesions in the peripheral nerves (In addition to treating the diabetes see p 150 for circulation stimulating exercises)
Gangrene *Ulcers* *Blisters*	These lesions are due primarily to the arteriosclerosis Infection is more frequent in diabetics Healing is slower if the diabetes is not under control Avoid ointments, which prevent drainage

CHAPTER 10

THE ADRENALS

ADRENAL MEDULLA

Function

The secretion of epinephrine (Fig 25) by the adrenal medulla follows stimulation via the sympathetic nerves The hormone acts on structures with sympathetic innervation, producing effects essentially identical with those following sympathetic stimulation The hormone produced following sympathetic nervous activity is therefore synergistic with the nervous stimuli This sympathico adrenal mechanism is

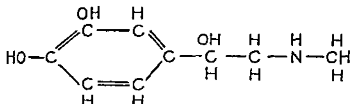


FIG 25—Epinephrine (adrenalin)

under a certain amount of control from the centers in the hypothalamic region rather than humoral control from the anterior pituitary The known effects of epinephrine include vasoconstriction bronchodilatation accelerated pulse, increased speed of coagulation of blood increased activity of intestinal muscle increased glycogenolysis in liver and muscle

if treatment of diabetes is prompt and thorough

High Red Cell Count — Due to dehydration, caused by acidosis

Leukocytosis — Seen in most cases of severe diabetic acidosis

Differential count is not different from that in infections, but does not mean infection

Blood Sugar — Level is high in untreated diabetes May be extremely variable when insulin is used (See pp 101, 108 and 140-144)

Blood Fat — In diabetic acidosis (ketosis) there is marked increase in the fat and cholesterol in the blood, making the serum creamy

Alkali Reserve — Decreased in acidosis Replenish by using normal saline or Hartmann's Physiological Buffer Solution or (more slowly) by feeding fruit juices

Function

The anterior pituitary gland produces an adrenotrophic substance, without a continuous supply of which the adrenal cortex may atrophy completely, with fatal results The adrenal cortex in turn produces a vitally necessary secretion containing probably two or more hormones The activity of adrenal cortex secretion is shown by maintenance of normal sodium, prevention of unduly high potassium concentration in blood plasma, maintenance of normal blood volume ability of the liver to maintain glycogen stores and to convert protein to dextrose, maintenance of muscular endurance and numerous secondary results from these fundamental processes It is possible that all these seemingly diverse functions may eventually be shown to depend on the catalysis of some one process With deficiency of cortical action a chain of symptoms arises and eventually the asthenia, toxemia and renal failure of outspoken Addison s disease lead to death

Diagnosis

The critically severe cases of adrenal insufficiency are diagnosed as *Addison s disease,* with profound asthenia hypotension, gastro intestinal disturbances pigmentation anemia and cachexia as the prominent symptoms The picture may be incomplete even though critically advanced Diagnosis is often confusing because of the numerous other causes which may give rise to one or more of these symptoms Laboratory

Diagnosis

There are no recognized clinical syndromes of hyperactivity or deficit of epinephrine save in the *paroxysmal hypertension* associated with tumors of the adrenal medulla Occasional patients with persistent hypertension have been found to have such tumors With diagnosis based on physical examination, exploration is advised when tumor is probable

Therapy

The use of epinephrine in medicine is largely to be classed as pharmacodynamic i e using an active biologic agent to secure or emphasize certain results for temporary ends regardless of etiology, as in the control of superficial oozing hemorrhage, the limitation of absorption of local anesthetics, relief of asthma, relief from hypoglycemia The doses vary from 0 3 to 1 c c hypodermically, and it is wise to avoid amounts larger than 0 3 c c until it is known whether the individual is sensitive to the hormone This sensitivity is greatly increased in thyrotoxicosis, and severe reactions may follow its use This is the basis of the Goetsch test for thyrotoxicosis, which is no longer considered clinically safe Epinephrine is not useful orally and is, in fact, disturbing to the stomach if included in oral medication Intravenous use of the drug is dangerous but intracardiac injection of 1 c c may be helpful in reviving a heart recently stopped from such causes as electric shock or drowning

with mean of 54 mg in 27 cases (Eight of the Addi sonian cases reported varied from 229 to 356 mg, mean 293 mg per 100 c c) The significant shift is the tendency to increased concentration of sodium and chlorine in the urine despite the lower blood serum sodium and chlorine in Addison s disease

Subsequently Robinson Power and Kepler reported on a safer and simpler technic for detection of the reduced renal function which is a consequence of adrenal insufficiency If the adrenal function is greatly reduced water diuresis fails and this can be checked by chloride loss and urea retention No special diet is used save that on the day before the test the patient is to have no salt added to his food and takes no food or drink after 6 00 p m Urine voided at 10 30 p m is to be discarded, and the night urine is saved from then until 7 30 a m After this he voids at hourly intervals up to 12 30 p m At 8 30 a m he drinks 20 c c water per Kg body weight taken within 45 minutes Only the volumes of the urine specimens need be recorded If diuresis follows so that the volume of any one of the hourly samples exceeds that of the night urine sample ad renal function is satisfactory

In case such adequate diuresis does not occur, the night urine should be analyzed for chloride and urea Blood should be drawn at 12 30 p m and plasma urea and chloride determined The results are to be expressed according to the following formula

$$A = \frac{\text{Urea in urine}}{\text{Urea in plasma}} \times \frac{\text{Chloride in plasma}}{\text{Chloride in urine}} \times \frac{\text{Largest vol of urine (1 hr)}}{\text{Vol of night urine (9 hr)}}$$

aids consist of the finding of lowered blood sodium, increased blood urea or nonprotein nitrogen and of calcium (late, in crises) and marked reduction in blood volume Save for the blood nitrogen determinations which are not, of course, specific, the methods required are not generally available Study of the mineral metabolism in 17 cases of Addison's disease led Cutler, Power and Wilder to conclude that under standardized conditions the concentration of urinary chloride was diagnostically more significant than any other factor easily available for study They outlined a procedure for testing suspected cases, with the distinct understanding that this is to be carried out under hospital conditions, for it may produce critical asthenic collapse, requiring emergency relief with intravenous saline and injections of adrenal cortex The procedure is essentially as follows

If adrenal cortex has been in use it is omitted for a day prior to beginning the test The diet is low in salt The routine suggested provides 0 95 Gm chlorine and 4 1 Gm potassium On the afternoon of the first day and the morning of the second day, the patient receives orally 42 mg potassium citrate per lb Water intake is generous On the second day the liquid intake is set at 40 c c per Kg, and on the third day it is 20 c c per Kg before 11 00 a m Urine is collected from 8 00 p m of the second day to 8 00 a m of the third day, and from 8 00 a m to 12 noon of the third day These specimens are examined for concentration of chlorine by standard methods Normal controls range from 17 to 141 mg per 100 c c

ical deduction Pathologic findings in adrenals following death from some of these conditions give support to the diagnostic assumption Treatment as for addisonian crises is known to be helpful and the addition of the recently available concentrated cortex extracts seems indicated

Therapy

Crises of *Addison s disease* call for prompt use of large and repeated doses of the best cortex extracts at hand The doses should be 10 20 c c intravenously, with smaller doses at intervals of a few hours intra muscularly or subcutaneously Accessory therapy should include the administration of repeated doses of saline intravenously, including dextrose to a minimum total of 100 Gm per 24 hours Maintenance therapy calls for the use of cortex in most severe cases and possibly for small doses in many mild cases in which the pigmentation anemia and cachexia are lacking In all cases increased intake of sodium salts is advisable, and sometimes this suffices without the use of the cortex. The sodium salts can be taken with greatest ease by use of 1 500 to 2,000 c c normal saline as the drinking water for each day Since there is a greater need for sodium than for chlorine, it may be still better to use a mixture of 2 parts sodium chloride with 1 part sodium citrate made up to about 1 per cent solution The diet should be designed to afford liberal sodium intake Recently advised special preparation of food to reduce potassium content seems unneces

This value A, is 30 or greater in patients without Addison's disease, but when it is 25 or less Addison's disease has usually been present The exceptions reported were in nephritics

Several independent trials of these types of testing have been reported, and experience indicates that they are dependable and the most simple ones in use It is possible that they may not reveal disorders of the adrenal cortex associated with such functions as carbohydrate metabolism, muscular strength and resistance to infections and intoxications With demonstration of more than one hormone produced by the cortex, such tests may reveal deficiency of the salt-metabolizing hormone only

There are probably many more cases with hypoadrenal activity of chronic types, in which the diagnosis of Addison's disease is not justified by conventional usage but in which the fundamental difficulty is similar but less marked No definite diagnostic terminology or criteria are accepted for such cases They are being increasingly considered as mild *hypoadrenia* Diagnostic separation from other types of asthenia and hypotension requires further study

There are a number of acute prostrating conditions which are receiving consideration as functional exhaustion or inactivation of the adrenal cortex Among these may be mentioned critical states in diphtheria and pneumonia, surgical or traumatic shock, peripheral vascular failure without cardiac failure The presence of all the phenomena of a crisis of addisonian type save lack of pigmentation leads to this clin

material Doses have to be determined by individual trial

Technical difficulties in preparing active extracts from pork adrenals have recently been overcome, and this tissue has been found unusually rich in the hormones This is especially true of the hormone which facilitates carbohydrate production from protein and storage of glucose as glycogen The discovery bids fair to make available far more potent adrenal cortex extract, and at a lower cost to the patient, thereby making possible maintenance therapy for some to whom it has not been available heretofore Unfortunately not all extracts, prepared by no matter what process are of even approximately uniform potency There has been a long debate about the appropriate bio assay technic to be applied to adrenal cortex extracts It now appears that there is no single technic which will suffice Probably two assays will provide measures of the two hormones, the so called salt-and water and the sugar hormones It is therefore expected that very shortly the appropriate authorities will be able to set up conditions by which investigators and manufacturers may agree on the potency of the products in use This will simplify a number of therapeutic problems in adrenal deficiency diseases Even now, it is possible for the clinician to insist that he will use no cortex extract which has not been assayed biologically

Prognosis—Addison's disease is usually progressive and fatal despite adequate therapy when the underlying pathologic condition is tuberculosis of the

sary The amount of improvement is too small in proportion to the dietary effort required Furthermore, because of reduced glycogen storage capacity, lunches between meals are often distinctly beneficial For reasons which are not yet clear, it has also been found helpful to include ascorbic acid (vitamin C) in 25 to 50 mg doses three times daily

Preparations Available—At present, the three dependable preparations on the American market are "Eschatin" of Parke, Davis and Company, and the adrenal cortex extract of the Upjohn and Wilson laboratories The relative potencies of these extracts cannot be stated with exactness, but the differences are not considered significant at this time The oral use of adrenal cortex in all save critical states is promising The production of stable and potent preparations has been marked by difficulties The 'Cortalex" tablets of Upjohn are valuable "Cortisorbate' pills of the Schieffelin Laboratory have been of low potency, but are being improved Capsules called 'Cortinoral" produced by the Harrower Laboratory have been distinctly beneficial to a number of patients with proved Addison's disease for long periods of maintenance therapy Other oral preparations have been tried, but commercial production is not yet under way It is important that all such oral adrenal cortex preparations be free from significant amounts of adrenal medulla since epinephrine irritates the stomach of some patients Recent results with oral therapy have made this type of treatment appear more economical than with injected

material Doses have to be determined by individual trial

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Prognosis—Addison s disease is usually progressive and fatal despite adequate therapy when the underlying pathologic condition is tuberculosis of the

adrenal glands plus tuberculosis elsewhere If the disease is limited to the adrenal glands or if the hypo function is due to adrenal atrophy, the prognosis is far better and justifies sustained therapy Such treatment may be worth while in asthenic cases with slowly progressing tuberculosis, in which adrenal underactivity is a handicap to the arrest of the tuberculosis There are remissions of adrenal underactivity, with consequent variations in the intensity of therapy required When the improvement under therapy makes it possible to omit the use of cortex extracts temporarily, long periods of observation will be required to determine whether real and lasting recovery of function has occurred Some of the results of therapy suggest that this may be a possibility Obviously it will require many years to determine the improved prognosis for Addison's disease under the increasingly adequate therapy now available (see Figures 26 and 27)

Synthetic Hormone Materials—The identification of a number of steroid molecules in extracts prepared from the adrenal glands has been accompanied by demonstration that several of these have no physiologic activity in maintaining adrenalectomized animals, but a few of these compounds are active in the same sense as crude extracts of the cortex One of these compounds, desoxycorticosterone, has been prepared synthetically and subjected to extensive clinical trials It has been found an effective substitute for cortex therapy so far as controlling salt metabolism and maintaining proper blood pressure are con

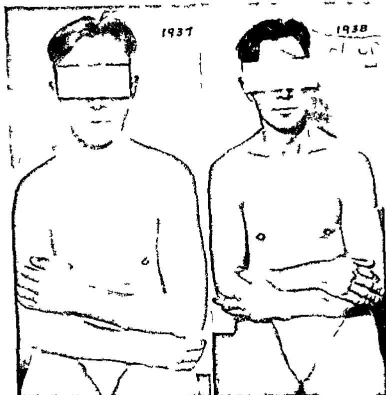


Fig 26 (left) —Addison's disease Norwegian 31 showed extremely dark skin with some pigmented macular spots on the torso The mucosae were similarly brown Symptoms included weakness poor endurance and gastro intestinal disturbances Hypotension was constant Symptoms were exaggerated by withdrawal of sodium in the hospital Active tuberculosis could not be demonstrated

Fig 27 (right) —Adrenal cortex therapy supplemented by salt and sodium bicarbonate produced consistent gain Maintenance became possible without use of the adrenal extract The decrease in pigmentation apparent here was confirmed by inspection

cerned The control of carbohydrate metabolism is not effectively provided by this steroid There are risks attached to use of desoxycorticosterone injections shown by accumulation of too much sodium and water and depletion of potassium, with hypertension and myocardial failure if the dosage is excessive The management of Addison s disease with desoxycorticosterone acetate requires daily intramuscular injection of 1 to 5 mg doses in oil The drug should be used with caution in older patients Extra salt feeding is seldom desirable and may lead to dangerous edema Potassium restriction should not be employed Hypertension or edema during therapy call for immediate interruption of the synthetic drug use of more potassium salts and return to natural adrenal gland extracts The great advantage of the synthetic compound is its lower cost as compared with current gland extract prices

The implantation of subcutaneous pellets of desoxycorticosterone acetate reported by Thorn, is an enticingly simple-sounding procedure It cannot be recommended for general use until more extensive experience with the method has been reported Perhaps other steroids will be found superior

The possibility of using adrenotrophic extracts of the anterior pituitary gland for the stimulation of atrophic or underactive adrenals has not been reported in clinical literature

The prognosis of acute shocklike states and post infectious exhaustions may be altered by the use of adrenal cortex therapy, coupled with the administra-

tion of saline, extra feedings and ascorbic acid Trials of this sort are being reported with encouraging results and no hazards Desoxycorticosterone does not appear useful in this type of treatment

VIRILISM, PITUITARY BASOPHILISM, CUSHING'S SYNDROME

It is often said that hyperfunction of the adrenal cortex is the basis for *virilism* in females or pseudo hermaphroditism The evidence for this is incomplete, based chiefly on the occasional association of the conditions mentioned with tumors of the adrenal cortex The present point of view is that these abnormalities may result from a dysfunction of cortical tissue or the secretion from atypical cells The tumors may actually be found in pituitary, adrenals thymus or ovary Most striking in the group of clinical types is the *Cushing syndrome* originally thought to be due to basophilic adenoma in the anterior pituitary but now known sometimes to be associated also with certain adrenal cortex tumors At times both are present, and the fundamental pathology may yet be the presence of atypical basophilic cells in the pituitary The syndrome includes obesity, hypertension tendency to reversal of sex type, purplish striations on the abdominal walls acrocyanosis, polycythemia and diffuse osteoporosis (See Figure 28) When regional signs do not indicate a pituitary tumor, then search for adrenal tumor by surgical exploration is advisable The prognosis untreated is grave but excellent results are

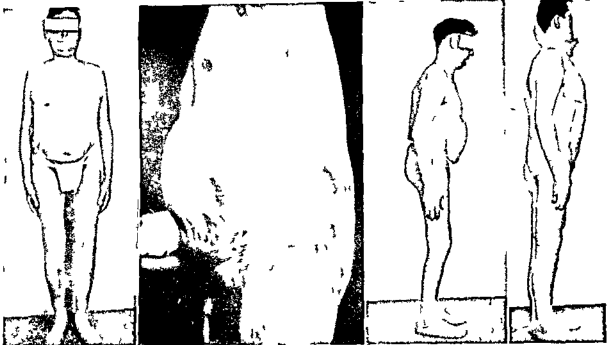


Fig 28 —Cushing syndrome (pituitary basophilism?) in man 23 Backache headache gain of 30 lb in 3 months acrocyanosis purplish striations on abdomen loss of 4 in in height constricting sensation in thorax loss of body hair visual fatigue photophobia inability to stand straight or work Marked hypertension plethoric complexion retinal sclerosis vertebrae decalcified with crushing of several centra causing loss of height and chest pains generalized demineralization of bones Sugar tolerance diminished Polyuria and polydipsia for 11 years suggested pituitary lesion as diagnosis but none could be demonstrated by eye examination At laparotomy adrenals appeared normal Subjective relief obtained for several months by high potassium feeding suggested by Dr Irvine McQuarrie because of possible

being reported in cases in which the tumor is in the adrenal and can be removed For pituitary tumors considered inoperable, deep x ray treatment is being tried

Compared with the number of patients seen with pituitary basophilism or with adrenal tumors, there are far more who have one or more of the following symptoms excessive hair on the face, limbs and torso irregularity of menstrual cycles sometimes reduced fertility, obesity and hypertension Of course any *one of these symptoms may occur without the others* or any two of them may be found together It is far from true that all women with an excess of hair have *menstrual irregularities or any reduction of fertility* Nevertheless the various subtypes of this syndrome demand attention So far exact studies of such women have not proceeded far enough to permit the construction of any adequate diagnostic classification or the prescription of therapy with assurance It is known that administration of estrogens internally or locally does not diminish the hirsutism The obesity is amenable to dietary therapy Hypertension is seldom extreme and tends to diminish with the loss of weight One of the most significant observations in many such women is the urinary excretion of the neutral 17-ketosteroids in moderately increased amounts Normal adult women excrete less than 10 mg daily whereas many hirsute women have been found to excrete a daily total of 15 to 20 mg This level of steroid loss is too low to constitute evidence of an adrenal car cinoma but it is thought to be due to an abnormality

of function of the adrenal cortex A few attempts have been made to resect a part of the adrenal tissue in order to treat the syndrome as a hyperadrenalism Poor results and a few catastrophes make this seem unjustifiable At present, no better solution can be offered than the best cosmetic treatment of the hirsutism management of the obesity and continued observation of the patients

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CHAPTER 11

OVARIES

Function

Increasingly exact study of the responses of animal ovaries to various pituitary extracts leads to the current hypothesis that there are three hormones which are gonadotrophic The follicle stimulator leads to growth and maturity of the follicle but does not bring about significant secretion of estrogenic hormone The luteinizing hormone probably in combination with the aforementioned material initiates ovulation and the formation of the corpus luteum The secretion of estrogen by the follicle and by similar tissue in the interstitial parts of the ovaries, as well as the secretion of progesterone by the corpus luteum are consequences of the third hormone spoken of as luteotrophin Perhaps this is identical with the lactogenic hormone from the anterior pituitary Quantitative studies in this field are still beset with difficulties but in such mathematical approach must lie the solution to numerous problems in the endocrine disturbances of the female reproductive system Exact details and absolute identification of separate hormones are not yet possible

The follicle produces a hormone known in general as an estrogenic substance and specifically named estradiol or dihydrotheelin The corpus luteum produces a hormone which is chemically closely related to estradiol, called progesterone Estradiol is respon

sible for the catalysis or stimulation of the following processes growth of the myometrium, development of the endometrium to the type seen at the end of the second week in the normal adult menstrual cycle, development of the adult vaginal mucosa,

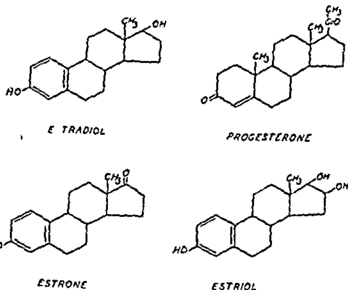


FIG 29 —This series of drawings and that in Figure 33 by Dr F C Koch

development of the mammary duct system sustaining of a rhythmic contraction of the uterus and the presence of the secondary sex characters, from libido to the character aspects which differentiate a mature female from a castrate The functions of progesterone are more limited this hormone brings about the alteration in endometrial type to the production of the secreting or progestational glands characteristic of the last two weeks of the normal adult menstrual

cycle (premenstrual endometrium) and also induces the development of acinar tissue in the breasts There is a tendency to oppose the activity of estradiol on uterine motility with less myometrial contraction as a consequence Further effects are not known The molecular structure is shown in Figure 29

The progesterone functions are evidently of special significance in preparing for the implantation of a fertilized ovum and in case of pregnancy the corpus luteum persists as a consequence of the production by chorionic tissue of a new hormone This substance is called the anterior pituitary like (A P L) hormone and was at first thought to be pituitary in origin It is excreted in large amounts in the urine of the pregnant woman The urinary loss decreases after the first trimester, possibly because by this time the placenta has taken over the production of large amounts of estrogenic substance and of progesterone These materials, now of placental origin, are sufficient for the development of the pregnant uterus and of the mammary glands to the point of lactation There is naturally a precipitate decline in the amount of these hormones post partum, and shortly thereafter the pituitary ovarian cycle is resumed During pregnancy A P L and the placental estrogenic hormone hold this pituitary ovarian cycle in abeyance The mechanism by which lactation tends to continue this inhibition is not yet understood

Estradiol is converted in part into estrone and estriol (or theelin and theelol) after which these substances are excreted in the urine as such and con-

jugated as glycuronates Most of the estradiol disappears without such excretion A large part of the disappearance of estradiol and estrone is attributed to changes in these *compounds brought about* by the liver The amount of excreted estrogenic material bears no known relation to the amount acting in the body Progesterone is converted to pregnandiol, conjugated similarly and excreted The determination of this excretory substance in the urine is thought to be a guide to diagnosis of adequacy of corpus luteum activity, and it may be found useful in determining the adequacy of progesterone therapy Details of this procedure have been reported in the paper by Venning and Browne (see References for Further Reading," p 195)

There are effects of estrogen and possibly also progesterone on the anterior pituitary Some of these apparently stimulate secretion, others inhibit it With two hormones produced by the ovaries and at least two by the pituitary, it is evident that one can expect on theoretic grounds several dozen different combinations of stimulative and inhibitory effects Until there are adequate methods for the quantitative determination of the amounts of these several hormones acting in an individual, it will remain a difficult puzzle At present, we may be sure of variation in the amounts of all these hormones at different times in the menstrual cycle These altered hormone concentrations are *therefore* believed to provide the mechanism for determining the intermenstrual interval, length of flow intensity of flow, degree of fertility and numerous

conditions referable to the effects of the ovarian hormones on vascular permeability, vascular tone and tissue hydration In the present state of partial knowledge any attempt to use ovarian products to stimulate or to inhibit pituitary activity must be considered entirely experimental

When the ovaries are removed or atrophy, the anterior pituitary usually secretes an increased amount of the gonadotrophic hormones This is especially well known for the follicle-stimulating hormone The assumption that the symptoms of the climacteric are attributable to the presence of such excessive amounts of gonadotrophic hormone in the body seems untenable for several reasons Relief from these symptoms does not require restoring the pituitary secretion level to its original intensity There is still speculation as to further disturbances in pituitary secretion at such times, since such phenomena as obesity acromegaly diabetes mellitus, thyrotoxicosis, arthritis and hypertension are unusually apt to appear at about this time of pituitary change These clinical changes cannot be interpreted as direct consequences of altered gonadotrophic secretion

Diagnosis

The variations of pituitary and ovarian activity are chiefly in the form of deficiencies rather than excesses The important exception is that following ovarian failure there is pituitary overactivity Only a few cases of primary or secondary *amenorrhea* which occur

before the climacteric age are thought to be due primarily to pituitary underactivity Some are caused by infectious or neoplastic disease acting directly upon the ovaries Many cases of amenorrhea are to be attributed either to failure in development of ovaries or to premature exhaustion The diagnostic differentiation of pituitary versus ovarian hypofunction as the primary etiologic factor is therefore of real importance and also of great difficulty Attempts to make these diagnostic separations by assay of blood and urine for the amounts of gonadotrophic estrogenic and progestational hormones have been diligently pursued To date the reliable methods are still so elaborate that they cannot be used outside research laboratories and the results are also susceptible of so much question in interpretation that these methods must still be left for the investigators Clinical dependence must remain on the use of the history, the physical examination and most urgently, the use of endometrial tissue obtained at predetermined times in the menstrual cycles (see Figures 30 and 31) The details of these matters occupy a large portion of the gynecologic texts and cannot be included here

In general, it may be said that histories of *primary amenorrhea secondary amenorrhea* (following after a few months or years of reasonably regular cyclic flowing) *scanty menstruation, irregular menstruation* and *menorrhagia* are all to be considered evidences of subnormal intensity of ovarian action Obviously, *sterility* may be a consequence of any one of these



Fig 30—Typical effect of the estrogenic hormone in human endometrium obtained at end of econd week in cycle

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Careful inquiry into the details of menstrual rhythm fertility and contraceptive practice still needs to be stressed A casual assertion of regularity of menses cannot be accepted at face value But even normal regularity is no guarantee of a fertile cycle marked by ovulation, for some cases of proved anovulatory flowing may occur in cycles of essentially four week type The details of history will often provide a more profitable lead in the study of a gynecologic endocrine problem than can be obtained from the physical examination

In the history, increasing attention is being devoted to the possible origin of the difficulty shortly after a pregnancy Except for infantilism and primary amenorrhea any of the syndromes mentioned may occur soon after a pregnancy The pathogenesis of this association may be logically considered in connection with the striking morphologic changes in the pituitary during pregnancy These alterations in anterior lobe cells are usually reversible, but at times there may be enduring residuals Most striking is the report of infarcts in the anterior lobe following a shocklike picture at delivery In this connection Sheehan provided human postmortem evidence of glandular alterations which can cause genital failure It is probable that less extensive infarcts or other types of damage in this area may be traced with increasing frequency when their possible significance is appreciated Consequently we must inquire not only into the time of onset of the gynecologic symptoms, but also we must search for other evidences of



Fig 31—Typical effect of progestin in human endometrium obtained at end of third week in cycle from same patient as in Figure 30

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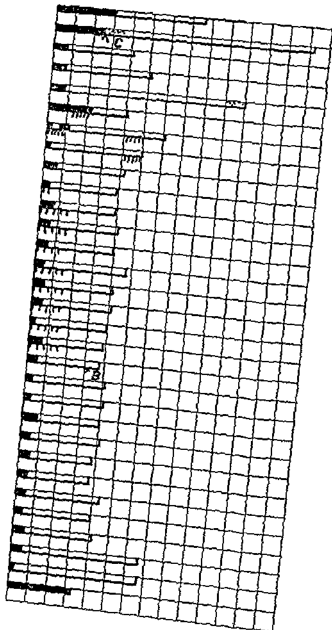
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disturbed anterior pituitary functions and for hypo thalamic symptoms For the latter growing field, ref erence should be made to the monograph of Ranson

Physical examination is helpful in discovering skin and hair changes resembling the masculine type, mammary underdevelopment or atrophy, the skeletal build characteristic of the early castrate and the obesity of the Froehlich type Pelvic examination is obviously of major importance Here positive find ings of uterine infantilism are sought, but found rather infrequently Cystic enlargement of the ovaries is a common result of long-continued, low activity of the pituitary If there are other pelvic findings, they are to be interpreted as anatomic, infec tious, neoplastic or traumatic problems and treated by gynecologic procedures before any endocrine approach is made But the examination is incomplete without tissue specimens in most of the endocrine problems The use of curet or endometrial biopsy instrument is increasing, but it should become still more widespread Obtaining the specimen of endo metrium is to be planned with care as to the time in

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Fig 32 (opposite) —Menstrual cycles in menorrhagic girl 17 Time intervals one week Total length of horizontal bars shows duration of menstrual cycles shaded areas duration of flows Curettage at *C* showed low intensity of follicle hormone (estrogen) stimulation. Endometrial biopsy at *B* showed typical progesterone action indicating that ovulation had occurred earlier in same cycle. Vertical lines indicate hypodermic injections of gonadotropic anterior pituitary extract (Prephysin) Note return to four week cycles moderate duration of flow and evidence of corpus luteum formation under treatment. After several months of reg ular menses recurrence of irregularity and of menorrhagia necessitated resumption of therapy A second relapse followed cessation of therapy at a later date



C
B

the menstrual cycle If it is obtained shortly before the appearance of the flow or during the first hours of the menses, the absence of the typical progestational changes will justify the diagnosis of failure of ovulation or anovulatory flowing If the tissue is obtained too early in the cycle, one can only speculate about ovulation and corpus luteum formation and secure an approximation about the intensity of follicular hormone activity from the extent of glandular development (Fig 32)

A more quantitative idea of the intensity of estrogenic effect may be secured from the examination of vaginal mucosa, by biopsy or most simply by the study of smears as described by Papanicolaou and Shorr Although the vaginal tissue does not contribute definite evidence of progesterone action, the type of epithelial cells does indicate the estrogen effect with sufficient certainty that one may follow increases from day to day whether estrogen is administered, as in the menopause, or the ovaries are stimulated by gonadotrophic hormone to produce more estrogen It is this technic which makes it possible to determine whether a given therapeutic program has promise, e g, in treating amenorrhea

As the *climacteric* approaches, the ovaries decrease in activity, ovulation is decreasingly frequent and the corpus luteum may be absent for long periods even though cycles of flow still occur The endometrial changes are no longer in the characteristic cycles but the simple tubular glands persist, their development is slow but may go on to dilated forms resembling

cysts and ultimately the endometrium is characterized by very few glands The vagina loses its adult thickness with a number of layers of epithelium and has an atrophic mucosa Frequently there appears a series of symptoms due to instability in the autonomic system including hot flashes, sweating attacks, palpitation dyspnea and vertigo and there may be paresthesias, exaggerated pain sense, insomnia and emotional instability Less often, there are the involutional mental symptoms in addition, including exaggerated worrying self-depreciation, melancholia jealousy and suicidal tendencies All these symptoms are recognized as consequences of ablation of the ovaries or of subsiding ovarian activity These disturbances do not occur in all women following cessation of ovarian secretion Reasons for this variability are unknown

The same clinical picture may occur in women younger than 40, even when there has been no destruction or removal of the ovaries Occasional cases of premature menopause are seen, but usually the syndrome is due to quantitative disturbances in the balanced relationship between the anterior pituitary and the ovaries In this group belong many of the cases of *menstrual irregularities* and of *sterility* There is as yet no diagnostic scheme by which the menopausal group may be separated from those patients in whom it may be possible to restore a normal and fertile cyclic function The clinical procedure should be to assume the climacteric nature of the syndrome when the circumstances of history and the uterine findings make this probable and when symptomatic relief is the ob-

jective If fertility is the desideratum, a therapeutic trial of methods which will stimulate the ovarian function is in order

Therapy

Anterior pituitary extracts are used to *stimulate ovarian development and function* For the purpose, only standardized preparations are to be employed Estrogenic hormone therapy is considered unwise when the objective is ovarian stimulation, for estrogens have various actions upon the pituitary, stimulating or inhibiting according to circumstances which cannot yet be defined

The first of these gonadotrophic substances tried was a concentrate from the urine of pregnant women (A P L) Constantly increasing evidence justifies the statement that this hormone has as its normal function the maintenance of the corpus luteum of pregnancy, but that in the nonpregnant woman it causes atresia of the graafian follicles and does not stimulate the human ovaries to ovulation and the formation of corpora lutea All the pituitary extracts so far available contain at least two gonadotrophic substances called follicle-stimulating (F S H) and luteinizing (L H) hormones These occur in varying proportions Known methods of assay do not allow quantitative determinations of the two when they occur in mixtures Consequently we must work at present with mixtures the composition of which we cannot be told Shortly, it will be possible to have extracts of these two hormones in separate solutions

for clinical trials We may anticipate superior results from more accurate prescription to fit the needs One further handicap has been the presence in all commercial products of proteins which are probably of no therapeutic importance but which cause painful local reactions and occasionally allergic manifestations

The protein content has been greatly reduced in the gonadotrophic preparations made from the serum of pregnant mares This substance is not identical with either the chorionic gonadotrophin of women or the hormones from the anterior lobe itself However, its physiologic effects most nearly resemble the pituitary hormone, and results indicate that this hormone may stimulate the human ovaries to ovulation and corpus luteum formation, with improved fertility The pregnant mare s serum (P M S) contains either two hormones as does the pituitary extract, or its hormone has both types of action Recently the low protein content of a few commercial pituitary extracts has made administration of these preparations in large doses safer

Much confusion has arisen from the variety of units employed by different manufacturers of gonadotrophic substances It is not possible to state an accurate comparison between any two of the three types pituitary, pregnant mare's serum and chorionic gonadotrophins The international unit of the chorionic material is now used for all accepted brands of the substance prepared from the urine of pregnant women, and commercial products may be used interchangeably, so far as potency is concerned. During

1939, the League of Nations authorized an international standard for the gonadotrophic substance prepared from pregnant mare's serum. This unit is smaller than any unit previously employed by commercial producers in the United States. The three commercial preparations of this type in use, Anteron, Gonadin and Gonadogen, are therefore comparable as to potency. To insure stability, two of these are prepared in dry form, to be dissolved at the time of use. The manufacturer of the other type claims that stability is insured by a special type of solvent used in the aqueous medium. Among the pituitary extracts for stimulation of the gonads, the unit employed by the manufacturers of Prephysin* is larger than that used by Armour or Ayerst, McKenna and Harrison for their Gonadotrophic (Maturity) Extract whereas other manufacturers are tending to choose units intermediate between these two in size. There is no agreement between manufacturers or any governmentally accepted standard method for deciding the relative values of these large or small units. With appropriate doses any of the pituitary or pregnant mare's serum preparations may be expected to accomplish similar results in stimulating the ovaries. Minimum effective doses will probably be found to be about 100 I. U. of mare's serum extract, 25 units of Prephysin or 200 units of Gonadotrophic Hormone

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* Reference to the product Prephysin in this volume signifies the anterior pituitary extract first devised by Fevold and Hisaw, standardized by its content of follicle stimulating hormone and known to contain [illegible] ng h mo[illegible]. Also originally produced and marketed by the Chappel Laboratories, [illegible] under the name of Gonatropе (Steraub) and [illegible] in 1945 [illegible] Gonadotrophin (Squibb). The activity is essentially unchanged but th[illegible] essential proteins have been almost entirely eliminated. A very similar product is Gonadophysin (Searle).

Because these materials are water-soluble, act quickly and continue to act for periods of hours only it is important that the hypodermic use of any such gonadotrophic extract be based on frequent small doses rather than larger amounts at longer intervals Therefore treatments for ovarian hypofunction are given daily The cyclic character of ovarian activity makes it important that such pituitary stimulation of the gonads should be intermittent The routine used by the author consists of a series of treatments beginning with the onset of menstrual flows, when it is known that the normal pituitary stimulation of the ovaries is increasing The series should be terminated at about the fourteenth day of the cycle when ovulation should occur

There have been a few reports of intravenous use of these gonadotrophic extracts in cases with evidence of follicular activity, in attempts to induce ovulation when this has not been occurring regularly For this purpose the doses have been from 800 to 1 200 I U of the hormone from serum of pregnant mares Results are difficult to prove Probably it will be necessary to follow this type of intravenous injection with hypodermic use of smaller doses of luteotrophic extract to support the secretory activity of the corpus luteum for a week, at the least Dosage for such purposes cannot yet be specified for it is still being tried experimentally The extracts available so far have been less effective and dependable in their luteinizing capacity than in stimulating follicle maturity

Results from such therapy with pituitary extracts

are secured in terms of months, not days, hence the difficulty in achieving clinically certain results which will convince either physician or patient However, the author has applied this type of procedure to *amenorrhea, irregular* and *infrequent menstruation, menorrhagia* and *sterility*, with promising results, especially in women who were characterized as *partially infantile*, i e, underdeveloped Such therapy should always be preceded by sufficient diagnostic study to make it certain that the fault is endocrine rather than infectious, neoplastic or nutritional

The employment of estrogenic substances clinically may be divided into two categories substitutional, and pharmacologic As an example of substitution, mention may be made of the treatment of gonorrheal *vaginitis* before adolescence by vaginal suppositories of this hormone Doses of 1,000 to 2,000 I U daily for courses of not over a few weeks have been found adequate Hypodermic or oral use of the preparations is less efficient The results are achieved by the maturation of the vaginal mucosa, as a consequence of which the usual acid producing secretion and flora appear, and the infection is thrown off The systemic as well as the uterine effects of estrogenic therapy are not seen or are minimal with such a procedure

Similar vaginal reaction may be secured after the climacteric if vaginitis, *kraurosis* and *pruritus* are severe enough to warrant the therapy Owing to the tendency of these atrophic changes to become the seat of malignant growths, such therapy must be carried on with caution, with repeated inspection of the

parts With dosage modest enough to merely relieve the atrophy, a healthier state of tissues may be maintained and probably greater safety secured for the patient than when no therapy is used

The use of estrogenic hormones in the *climacteric* syndrome serves the purpose of substitution also The ovarian hormones do not stimulate ovarian activity, they inhibit it But in the climacteric, the objective is relief from symptoms, not maintenance of function Therefore the doses of estrogenic hormone should be made adequate for symptomatic control Restoration of bleeding is undesirable but not dangerous Other limiting factors on size of dosage are stimulation of mammary enlargement or increase of libido to an uncomfortable degree Whenever either of these occurs, the dose should be sharply reduced until the undesirable symptoms are past It may then be increased to a slightly lower level than was in use when the mammary lumps or increased libido appeared

The estrogenic therapy may be hypodermic (aqueous), intramuscular (in oil), by vaginal suppository (in hardened gelatin) or oral (solid or in oil) The aqueous hypodermic preparations have all but disappeared only to be replaced by aqueous suspensions of microcrystals The vaginal suppository method is no longer used save for vaginitis and concentration on local effects The oil injections are widely used at present The author has repeatedly protested because this involves the frequent introduction of foreign oils (peanut, sesame and corn oils are used), and these

foreign oils are not absorbed but may remain indefinitely where they are injected Sometimes foreign body reactions occur

Oral therapy is adequate for all the results desired, as proved by either symptomatic response or tissue changes The dosage must be varied to fit the patient Daily therapy or even better, the division of the dose into two or three portions daily is of benefit in sustaining the action The amount required varies from 16,000 I U down to as little as 500 units daily, in oral use Intramuscular injections are given at longer intervals with less uniformity of control and in doses of 1,000 to 10,000 units at intervals of two to 14 days The therapy should be pushed to the point of complete control of the autonomic symptoms within two to three weeks After this, the dosage may be gradually reduced until the minimal level is attained at which control remains adequate It will be found that further gradual reduction may be attained during succeeding weeks or months and complete cessation of the hormone treatment may be anticipated after six months to five years The duration of climacteric symptoms is probably reduced by sustaining the treatment at an adequate level at all times Infections emotional stress and hot weather are all prone to increase the symptoms and may require a temporary increase in dosage to retain control Failures in the relief of both the autonomic and the psychic symptoms have usually been traceable to inadequate dosage In psychoses it is of course important to use other psychotherapy as indicated Sedatives do not

appear advisable save in acute emergencies The use of estrogenic hormone to control the emesis of pregnancy, to prevent toxemias of pregnancy, to relieve dysmenorrhea or to reenforce the action of oxytocic posterior pituitary hormone is all a matter of gynecologic and obstetric research at this time

The American preparations of estrogenic hormones which are of standardized and dependable potency are so numerous that their enumeration will not be attempted They can be grouped into a few preparations of estradiol (dihydrotheelin), which is usually injected as the benzoate or the propionate, three brands of estrone (theelin) three brands of estriol (theelol) and a large number of preparations which are now called 'Estrogenic Substance' This last term has been adopted by the Council on Pharmacy and Chemistry of the American Medical Association for preparations made from urine usually of pregnant mares and composed of more than 90 per cent estrone together with several other naturally occurring and synergistic estrogenic compounds The unit for standardization of estrogenic substance is provisionally the same as that used for estrone This introduces some error but this is the best approximation possible so far By definition of the Health Organization of the League of Nations (1932) 1 mg estrone is 10 000 I U There is also a standard for estradiol as the benzoate of which 1 mg is also 10 000 I (benzoate) U These two types may therefore be prescribed in terms of units or of milligrams Since estrogenic substance is a mixture of

foreign oils are not absorbed but may remain indefinitely where they are injected Sometimes foreign body reactions occur

Oral therapy is adequate for all the results desired as proved by either symptomatic response or tissue changes The dosage must be varied to fit the patient Daily therapy or, even better, the division of the dose into two or three portions daily is of benefit in sustaining the action The amount required varies from 16 000 I U down to as little as 500 units daily, in oral use Intramuscular injections are given at longer intervals with less uniformity of control and in doses of 1,000 to 10 000 units at intervals of two to 14 days The therapy should be pushed to the point of complete control of the autonomic symptoms within two to three weeks After this, the dosage may be gradually reduced until the minimal level is attained at which control remains adequate It will be found that further gradual reduction may be attained during succeeding weeks or months and complete cessation of the hormone treatment may be anticipated after six months to five years The duration of climacteric symptoms is probably reduced by sustaining the treatment at an adequate level at all times Infections emotional stress and hot weather are all prone to increase the symptoms and may require a temporary increase in dosage to retain control Failures in the relief of both the autonomic and the psychic symptoms have usually been traceable to inadequate dosage In psychoses it is of course important to use other psychotherapy as indicated Sedatives do not

from large doses The question of slowly developing toxicity from sustained treatment with this synthetic material led to a delay in official acceptance of the drug in the United States, but in late 1941 this was accomplished It is now considered safe to employ under professional supervision as a substitute for naturally occurring estrogenic materials Diethyl stilbestrol, familiarly spoken of as stilbestrol is active whether given parenterally in oil or orally and there is so little loss of potency when it is ingested that this is the route of choice in most patients Dosage varies from 0 1 to 5 mg daily, with few patients requiring more than 2 mg The greatest advantage of this substance is its low cost Its greatest handicap is the tendency to provoke nausea whether given orally or parenterally Many methods have been tried to eliminate the nausea So far the best is merely to start with small doses, increasing gradually to that amount which produces optimal results, which can usually be achieved without nausea If nausea is an obstacle naturally occurring estrogens must be substituted

Progesterone therapy is limited to relief from *dysmenorrhea,* and prevention of *repeated abortion* Doses are still being determined and vary from 1 unit to 2 units at intervals of one to two days Probably the successes will become more frequent when larger doses, such as 3 to 5 mg, are given daily During pregnancy there must be well over 20 mg per day produced in the healthy maternal organism Successful treatment of dysmenorrhea with small doses is

somewhat variable composition, it can be prescribed only in terms of units, which are biologically comparable to those of estrone Their clinical effectiveness parallels this biologic standardization

Emmenin is a term used by Ayerst, McKenna and Harrison for a preparation composed of estriol in the form of the glycuronide obtained from the placenta, and standardized in what the manufacturers call ' day oral units " It is used in tablet form, orally, and since it has been made available in higher concentrations per tablet is useful in many cases with moderately severe symptoms This preparation is now being replaced gradually by a far more potent preparation of estrogenic material, called Premarin, manufactured from the same sources as the usual estrogenic substance but in a manner to preserve much more biologic activity for oral use At present, Premarin is dispensed in tablets standardized by weight of the estrone sulfate content, the principal ingredient

There are numerous other preparations which are unstandardized or with concentrations not so well established It is again urged that clinical use of estrogenic hormone should be limited to accurately standardized products

Diethylstilbestrol is the name of a synthetic compound produced by Dodds and associates in a deliberate search for estrogenically active molecules This has been used in animal and human therapy, and is known to manifest essentially all the types of biologic activity characteristic of the naturally occurring estrogens There has been some evidence of toxicity

known to contain only the estrogenic hormone, in variable amounts, or small and variable amounts of progestational activity, rendering them undependable for human therapy A synthetic compound closely related to both progesterone and testosterone is called pregneninolone and has two advantages It is far more active when taken orally than either of these other compounds, and its activity is closely similar to that of progesterone, although doses must be 10 to 20 times as large as those of progesterone It is being used experimentally for oral therapy as a substitute for progesterone with much promise of success

Testosterone has been used with much enthusiasm *in recent years for treatment of many types of gyneco-*logic disorder Results vary from excellent to poor The effects are due to inhibition of pituitary function, atrophy of endometrium or paradoxically to the maintenance of certain endometrial stages attained under the influence of ovarian hormones The risk of stimulating masculine characteristic activity such as beard growth change in laryngeal structures with deeper pitch of the voice and skin pigmentation seems sufficient to warn most clinicians against using testosterone in women The results claimed can be secured with gonadotrophic extracts estrogens and progesterone

Prognosis

The prognosis for patients with retarded development of ovaries is still indeterminate but results indicate that some can achieve sufficient improvement to

hard to explain Only small series have been reported It is evident that progesterone is far from being a panacea for dysmenorrhea The mechanism involved in relief of pain before or during menstruation or of postpartum pains is debatable Relief from pain is frequent and surprisingly prompt The cost is the limiting factor at present The usefulness of this material to prevent abortions is by intensifying the progestational development of the endometrium and reducing the contractility of the myometrium The hormone is being employed when there is a history of repeated abortions in the first trimester It is questionable whether progesterone is of benefit after bleeding has begun, with threat of impending abortion Doses should be ample, 1-5 units daily, with gradual reduction, and should be continued through the fourth month of gestation After this time the placental production of progesterone is depended upon The use of vitamin E, as wheat germ oil, in these conditions is being recommended also, but its action is still more obscure

Progesterone is available as Progestin' (Upjohn), Proluton (Schering Corporation) and "Lipo-Lutin' (Parke, Davis and Company) Other similarly standardized products are being introduced on the American market by other firms One international unit is 1 mg progesterone All these are in oil solutions for intramuscular injection The hormone is poorly soluble in water and is rapidly destroyed when exposed in water to the air Aqueous preparations of the corpus luteum have long been used but are now

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allow of regular cycles and fertility Whether therapy will have to be sustained or not, cannot be predicted In the climacteric, the prognosis is simpler The climacteric syndrome itself is not permanent, and when untreated it is variable in duration, but difficulties lasting 10 years are not uncommon, and some of 15 to 25 years' duration have been reported Under therapy, this period can be abbreviated to not over five years usually, with relief of all of the symptoms afforded at the same time Prognosis from use of progesterone is still indeterminate, owing to the brief experience with it

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tissue is benefited by the presence of testosterone so that one portion of the gonad is helpful to the other, and the effect is shown by maintenance of a certain amount of spermatogenic activity in animals hypophysectomized but given testosterone The application of this relationship in the human is not yet clear

In relief from castration changes in the male, testosterone acts similarly to estrogenic hormones employed in the female but doses necessary for comparable effects are larger Whether use of the spermatogenic tissue hormone would be better, can only be conjectured at this time

The whole problem of prostatic hypertrophy must be held in reserve for although testicular hormones are necessary for prostatic development it is not possible to state what prostatic hypertrophy is

Large doses of testosterone are known to inhibit the production of gonadotrophic hormones by the anterior pituitary, thereby causing secondary underactivity of the testicles Testosterone is therefore considered contraindicated when the testes are to be stimulated This same activity of testosterone has been demonstrated in the female as a consequence of which ovarian activity may be inhibited Testosterone has been used therapeutically for many types of gynecologic problems Although symptomatic relief may be attained this method is questionable for two reasons (1) it tends to decrease although temporarily the function of the gonads and (2) if the doses are large masculine features may appear Testosterone therapy in the female is therefore not recommended

Chapter 12

TESTES

Function

The anterior pituitary produces the same two hormones in male as in female The one designated follicle-stimulating in the female is responsible for development and function of the spermatogenic tissue and the luteinizing hormone for the development and function of the interstitial cells It is believed that the spermatogenic cells produce a hormone which has not been isolated in pure form or been identified with

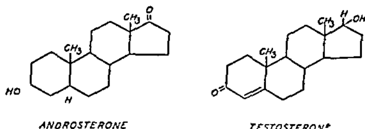


FIG. 33—Testicular hormones

certainty by its physiologic functions The interstitial tissue produces testosterone, a hormone which is chemically similar to progesterone and estradiol, the ovarian hormones (Fig 29) These chemical similarities do not prevent the "male hormone' from having highly specific effects on the prostate seminal vesicles, hair pattern and secondary sex characters It is known that testosterone does not substitute for all the testicular hormone effects The spermatogenic

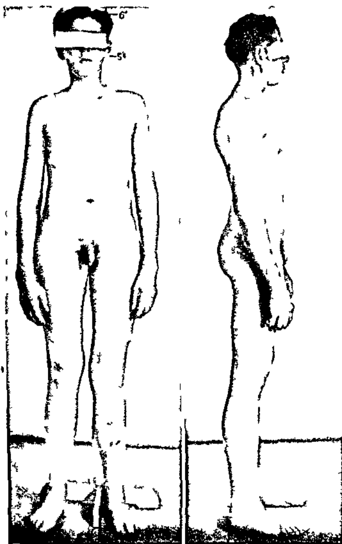


Fig 34—Eunuchoid type age 27 Testes had been in scrotum but exceptionally small at 17 Growth normal to thirteenth year slow to 18 fast to 21 when height of 71¾ in and span of 75 in were attained Voice occasionally shows tendency to low masculine register No x ray evidence of skull lesion Hypodermic injections of anterior pituitary extract (Prephysin) for several weeks caused no detectable growth of testicular tissue Exploration of inguinal canal failed to reveal any testicular tissue

Diagnosis

Evidence of underactive testes is deduced from small size of testes and other genitalia, delay in development of sex characters (*infantilism, Froehlich syndrome*), reduced fertility and the climacteric syndrome The last resembles in all important details the syndrome as seen in women but is less frequently met clinically Definite objective evidence about hormone action in the male is not easily available since there is no technic comparable to examination of the vaginal mucosa or the endometrium and the phenomena of sex activity are so much more subject to psychic effect than is menstruation At present, diagnosis must be by history and physical examination, with elimination by urologic study of infectious and neoplastic problems The recent work of C G Heller shows that the climacteric syndrome in males is marked by a great increase in urinary gonadotrophic excretion as is the female climacteric This fact may serve as a diagnostic criterion when the clinician has adequate laboratory facilities

In several clinics where careful investigation of male patients with disturbances of reproductive function is under way, biopsies are being taken from the testes by small incisions in the scrotum under local anesthesia In the hands of competent urologists this is apparently a far simpler process than was once thought, and the tissues thus obtained are disclosing some unexpected syndromes in the male Failure to develop, atrophy scarring from several infectious processes and failure of one part of the testicular tissue

without comparable damage to other structures are among the findings The studies have not gone far enough to justify detailed description in this volume The approach by means of objective study of testicular tissue is probably a step in the direction of rapid progress comparable to that produced by the use of endometrial biopsies in women

Aside from complete and general destruction of the testes, the chief differentiation to date has been that by Heller and Nelson who showed that associated with hyalinization of the tunica propria and failure of spermatogenesis there are subtypes depending on more or less extensive failure of the functions of the Leydig cells The evidences of the tubular failure are sterility and azoospermia Leydig cell failure leads to defects in complete masculine development These are variable in degree and not all are necessarily seen in any one case Specifically, there may be delays in bone maturation with variable degrees of eunuchoidism, genitalia may be small hair distribution may be atypical for the male voice pitch may be high musculature may be subnormal and gynecomastia may be found The excretion of 17-ketosteroids tends to be low Biopsy shows varying amounts of disturbance in the Leydig cells Symptomatology may include, in addition to the obvious consequences of the aforementioned conditions complaints typical of the climacteric syndrome especially in patients over 25 In all of Heller and Nelson s cases gonadotrophin excretion was significantly increased as it is also in the climacteric Etiology was not clear, but history of infectious processes

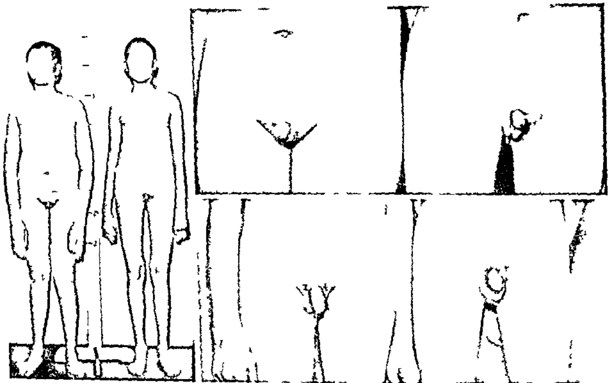


Fig 35.—Sex infantilism in brothers 24 and 28. Note long arms and legs, broad pelvic girdles. Progress in development of external genitalia during one year of therapy with gonadotrophic extracts of pituitary, pregnant mare's serum and chorionic gonadotrophins used in turn

of pregnancy urine for this purpose seems less well founded, for this hormone does not directly stimulate the spermatogenic tissue, although it does affect the interstitial cells

Apparently it is due to this latter result that pregnancy urine therapy has so often led to descent of *cryptorchid glands* with enlargement of the testes at the same time Genuine pituitary therapy may be expected to stimulate both types of cells and secure a more nearly natural testicular development Development as well as descent is the real objective of therapy This should not be pushed so rapidly that precocious adolescent changes appear The administration of anterior pituitary hormones to stimulate the male may be daily, since there is no cyclic action of the testis to be taken into consideration Doses of extract will have to be increased gradually by trial to secure results Failure of descent of the testis after doses adequate to stimulate the growth of the gland will necessitate surgery This is inevitable in a fair proportion of patients with cryptorchidism With testes in the scrotum and the patient past the age of beginning adolescence therapy may be more intense, if needed to secure testicular stimulation (See Figure 35) However, the field has not been studied sufficiently to allow final recommendations as to details of dosage Employment of Prephysin in doses of 1 c c daily (25 units) is not excessive With pregnancy urine preparations, the units are of different value and doses vary from 50 to 500 units daily The duration of *treatment must be decided by the progress*

was common enough to be considered significant, even prepuberal mumps being a possible factor An unexplained degenerative process is also suspected as a cause

The one type of therapy which has been found useful has been substitution with testosterone Dosage has been rather large—25 mg of the propionate parenterally as often as five times weekly, or implantation of 75 mg pellets of pure testosterone The use of methyl testosterone orally was not successful Results achieved by such substitution were those that might be expected in climacteric or eunuchoidal patients and did not give evidence of restitution of spermatogenic functions

Therapy

For *underdevelopment of testes* and genitalia, the obvious treatment is the hypodermic injection of the anterior pituitary gonadotrophic hormone Prephysin* or the Gonadotrophic (Maturity) Pituitary Extracts (Armour or Ayerst, McKenna and Harrison laboratories) are the well standardized anterior lobe preparations on the American market Others are being introduced The concentrates from pregnant mare's serum Gonadogen (Upjohn), Gonadin (Cutter) and Anteron (Schering), or the Danish Antex (Leo), are probably effective stimulants of testicular tissue growth and function The use of the extracts

* Reference to the product Prephysin in this volume is [illegible] the anterior pituitary extract first devised by Fevold and Hisaw standardized by its content of follicle stimulating hormone and known to contain [illegible] hormone also Originally produced and marketed by Chappel Laboratories [illegible] been produced under the name of G[illegible] (Stearns) and beginning in 1945 [illegible] produced under the name of Gonadotophin (Squibb) The activity [illegible] essentially unchanged but the [illegible] and unessential protein have been almost entirely eliminated A very similar product is Gonadophysin (Searle)

propionate Since such therapy with either male or female hormones leads to testicular atrophy (as it does to ovarian atrophy) it should not be employed if the testicles are simultaneously being stimulated or their function is to be preserved

The effects of testosterone on reduced libido and impotence are uncertain These symptoms are complicated phenomena, often with psychic backgrounds Testosterone does stimulate the secondary sex characters and will tend to increase libido insofar as the physical situation is responsible

Testosterone is commercially available in America as "Oreton (Schering), 'Perandren (Ciba) and 'Neo-hombreol' (Roche Organon) Modifications of these proprietary names are made for different esters and for the orally active methyl testosterone

Prognosis

Use of these materials in the male is too recent to justify statements of prognosis under therapy Testicular descent has been produced in a large percentage of cases from use of A P L and also genuine pituitary therapy The need for continued use of pituitary stimulation is still to be determined Use of androgenic hormone must be continued if the results are to be sustained

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attained Usually descent of cryptorchid glands can be expected in a few weeks If there is no evidence of progress under therapy, the dosage should be rapidly increased at intervals of only a few weeks, until as much as 500 units per day has been tried for two weeks If palpable testicles are then present in the canals, but do not descend to a scrotal position, surgery should be planned Perhaps one of the great merits of this therapy for cryptorchidism is that it serves to determine which cases will allow descent and which require surgical removal of the anatomic barriers Numerous commercial preparations of the chorionic gonadotrophic hormone are now available tending to be standardized in the international unit sanctioned by the Health Organisation of the League of Nations Such extracts from pregnant women's urine are usually more quickly productive of testicular descent than are the pituitary extracts They must be used with caution as to dosage and duration of therapy to avoid unduly large genitalia

For treatment of *climacteric* difficulties, testosterone has been helpful in relieving autonomic symptoms but is more promising in control of the involutional mental problems Testosterone must be given in oil injections, intramuscularly, in doses of 5 to 25 mg at intervals of one day to one week The disadvantages of foreign oil injection make it important to find other ways of administering this hormone The production of methyl testosterone has made possible oral therapy, using 10 mg tablets one to four times daily as an acceptable substitute for injected testosterone

relationship that characterizes pediatrics as a part of internal medicine

GROWTH

In addition to the obvious need for protein and fuel foods to sustain growth we have become increasingly aware of the participation in this process of most of the vitamins It is not possible to designate one vita min as predominantly growth promoting At this time we can only urge the intake of an abundance of vitamins, without being able to state with certainty the minimum quantities of any vitamin necessary for life for average health or for the best physical condition Such current recommendations of optimal vitamin intake as those from the Food and Nutrition Board of the National Research Council admittedly provide a margin over and above demonstrated minimal needs We are not in a position to state the varying needs of the body for any one vitamin if there is short age or excess of some other nutrient Until pre scriptions can be written in definite terms we must accept as clinical standards of dietary adequacy the experience of careful students of pediatrics When in doubt, it is wise to increase the intake of milk, up to 1 qt daily make certain of the use of egg and meat food daily, introduce liberal amounts of un cooked fruits emphasize the use of succulent and green colored vegetables and frequently augment the diet with concentrated forms of vitamin D Such a nutritional approach should be the first item in study of any child with retarded growth

Chapter 13

ENDOCRINOPATHIES IN CHILDREN AND ADOLESCENTS

In a discussion of biologic processes strikingly characteristic of children one should mention (1) growth, (2) metamorphosis (3) increasing balance of dynamic processes and (4) increasing immunity to infectious processes The endocrine glands are involved to varying degrees in all these phenomena, therefore there is especial importance in endocrine therapy in childhood and adolescence In none of the aspects of the first two decades of life can we consider these endocrine responsibilities aside from the other forces involved, such as heredity, nutrition environment (economic educational, infectious) and the regulatory activities of the nervous system Let it be emphasized again that hormones must be thought of as catalysts which modify the speed of chemical reactions and biologic activities, as parts of an elaborate mechanism for the smooth coordination of these features of life by the communication of appropriate impulses It is, therefore, suitable to consider therapy with endocrine materials in the early years of life in terms of these fundamental general processes rather than as special applications of the individual hormone substances Obviously the endocrinology of childhood bears to endocrinology in general the same

relationship that characterizes pediatrics as a part of internal medicine

GROWTH

In addition to the obvious need for protein and fuel foods to sustain growth, we have become increasingly aware of the participation in this process of most of the vitamins It is not possible to designate one vitamin as predominantly growth promoting At this time we can only urge the intake of an abundance of vitamins, without being able to state with certainty the minimum quantities of any vitamin necessary for life, for average health or for the best physical condition Such current recommendations of optimal vitamin intake as those from the Food and Nutrition Board of the National Research Council admittedly provide a margin over and above demonstrated minimal needs We are not in a position to state the varying needs of the body for any one vitamin if there is shortage or excess of some other nutrient Until prescriptions can be written in definite terms we must accept as clinical standards of dietary adequacy the experience of careful students of pediatrics When in doubt, it is wise to increase the intake of milk up to 1 qt daily, make certain of the use of egg and meat food daily, introduce liberal amounts of uncooked fruits, emphasize the use of succulent and green colored vegetables and frequently augment the diet with concentrated forms of vitamin D Such a nutritional approach should be the first item in study of any child with retarded growth

It is assumed that the wide diffusion of information about nutrition in the past three decades has been responsible in large part for the fact that the stature of adults has increased in the United States during that time This increase has been recognized in the ultimate height of young adults and also in the greater height attained at any given age by growing children Especially does the latter factor serve to render the older tables of height for age undependable in detecting small deviations from the norm Better criteria for dwarfism or gigantism should be based on the rate of growth, or the increment per year Too often this information is not available, but periodic health examinations, school nurses' records and lay interest are contributing to improved data about children If doubt exists, records of growth should be kept over a period of eight to 12 months to determine the child's status before endocrine therapy is advocated Such measurements must be made with rigid scales and with shoes removed If small gains are to be determined accurately, even the usual diurnal variations in height should be avoided by measurement at the same time of day, preferably in the morning

When no nutritional fault can be identified as a cause of retarded growth the history must be studied further as to possible familial factors or severe, repeated or chronic infections which may have provided a handicap Lacking any of these as reasonable causes for small stature the anterior pituitary is assumed to be underactive One must not forget that untreated hypothyroidism inadequately managed dia-

betes mellitus and chronic parathyroid disease are also endocrine factors which may interfere with normal growth But even granting that all these possible causes can be eliminated by thorough medical examination, it is still only a presumptive diagnosis when hypopituitarism is diagnosed as the cause of dwarfism This need not interfere with a therapeutic program of injecting potent growth promoting pituitary extracts These materials stimulate the anabolic processes by which dietary protein is converted into tissue protoplasm accompanied by the addition of other characteristic dietary materials as in the deposits of calcium and phosphorus in the growing bones From skin to bones, our tissues are living changing building and breaking down protoplasm throughout life The characteristic of growth is that the formation of new tissue (anabolism) is more rapid than the destruction of tissue (catabolism) The pituitary extracts generally spoken of as growth promoting might better be described as protein anabolic stimulants The result of this activity on bones leads to formation of longer bones—and resulting greater stature—before bony union of the epiphyses makes further growth in height impossible At the same time that bones are growing longer this anabolic catalyst increases the growth of muscles viscera etc The clinical applications of this broader function of the pituitary growth hormone have not been explored Their pathologic exaggeration is illustrated by the processes of acromegaly, which can occur only after adolescence has led to closure of the epiphyses

Administration of growth promoting pituitary extracts should not be undertaken in late childhood, or more especially in adolescent patients, until x-ray films of the ends of the femur show that epiphyseal union is incomplete enough to make significant gain in stature possible With the moderate dosages usually used, the danger of causing acromegaly is not so great as is the folly of useless therapy The rate at which pituitary material is to be given depends on the increase in rate of growth desired and on the time available before epiphyseal union must be anticipated These extracts are water-soluble and they act quickly and briefly, wherefore it seems reasonable to administer them daily rather than at longer intervals Since there is still no uniform method of standardizing such extracts, one must be guided by the manufacturer's suggestions Of the several extracts with which the author has had experience, daily doses of 1 c c are advised, although smaller doses may be used when slow effects are preferred, and 2 c c doses have been used with apparent profit occasionally This recommendation applies to the preparations from the Armour, Squibb, Wilson and Parke, Davis laboratories Such therapy may well continue until growth has reached the usual stature for the age or closure of epiphyses precludes further growth The importance of early treatment must be impressed on parents Occasionally late treatment may help if one can demonstrate delayed union of the epiphyses as in the case illustrated in Figures 5-9

The converse picture of gigantism is more difficult

to diagnose and treat The primary task is to predict with any certainty that a particular child who is growing at an unusually rapid rate will ultimately become taller than normal Merely charting the growth rate carefully will not indicate the ultimate probable height, *for union of the epiphyses is not conditioned* by height or time factors The forces which have been identified as definitely accelerating epiphyseal closure are two which make for metamorphosis from juvenile into mature types thyroid and gonad hormones The development of centers of ossification and their ultimate incorporation into adult bone can be followed by x ray studies and comparison with adequate standards, such as those of Todd *et al* and of P C Hodges, is one of the best methods of evaluating the intensity of thyroid secretion during childhood and early adolescence In some way which can be specified with much less accuracy we recognize that the ultimate union of the growing areas in the bones is accelerated by marked increase in production of the sex hormones by the gonads during the early teens It is theoretically possible that gigantism may be checked by administration of thyroid, the appropriate sex hormone, or the gonadotrophic hormone of the pituitary to induce more rapid maturation of the child Administration of the latter is a particularly interesting possibility since the processes leading to gigantism (or dwarfism) are probably expressions of relative disproportion between the growth-stimulating and the gonad stimulating factors of the pituitary Such procedures have no background of dem

onstrated clinical results but they are probably without serious risk. An example of a patient with "gigantism" treated in this way is shown in Fig 36 Attempts to retard growth by the use of x ray therapy to the pituitary must be condemned because of the possibility of damaging other pituitary functions if any effect at all is achieved

As a corollary to the influence of thyroid secretion on the union of epiphyses, a precaution must be mentioned about use of thyroid therapy together with pituitary extracts for stimulation of growth If low basal metabolism, delayed bone age by x ray and high blood cholesterol determinations indicate hypothyroidism, all clinicians would agree that the use of thyroid is definitely indicated But prescription of thyroid as a nonspecific 'general stimulant may hasten union of the epiphyses and reduce the amount of growth obtainable by prolonged anterior pituitary therapy

PRECOCIOUS ADOLESCENCE

Most cases of unusually early adolescence or pubertas praecox have been assumed to result from tumors of the pituitary, pineal thymus, adrenals or gonads These have been dramatic cases and often have been "cured by surgical extirpation of the tumors However there are many children with this unfortunate syndrome in whom no neoplastic process has been found They probably represent merely a disproportionately rapid stimulation of the metamorphosis to reproductive maturity before the growth

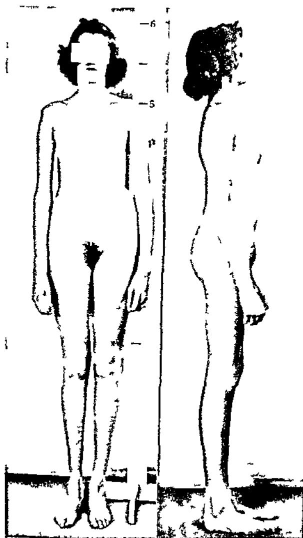


Fig 36—Adolescent gigantism age 13 with menarche at 12 During treatment with thyroid and pituitary gonadotrophic extract epiphyses completed union the following year with slight further growth in stature

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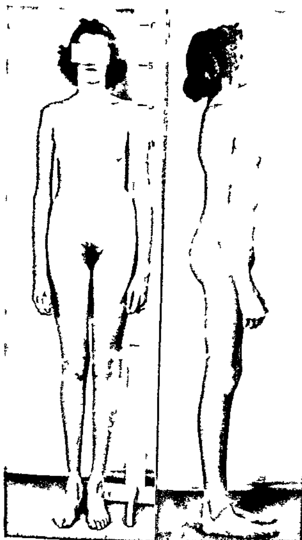


Fig 36—Adolescent gigantism age 13 with menarche at 12 During treatment with thyroid and pituitary gonadotrophic extract epiphyses completed union the following year with slight further growth in stature

impulses have resulted in conventional standard stature These individuals tend, therefore to become dwarfs, although they are tall for their age in early years The anatomic source of the stimuli leading to precocious metamorphosis and growth has not been identified The probability is in favor of an early increase in the activity of the anterior pituitary but participation of the adrenal cortex cannot be eliminated The tendency of these children to be excessively tall for their age lends force to the argument for pituitary responsibility Another possibility must be kept in mind—that of increased sensitivity of the gonads to stimulation In small experimental animals it is impossible to induce puberal changes in the earlier weeks of life but after a critical period, such as about 20 days in the rat pituitary extracts will induce premature puberty In children who show precocious puberty there may be increased sensitivity to the normal stimuli

Treatment of the condition should begin with a careful search for tumors of the pituitary thymus adrenal or gonads If none can be found after study for several months, exploration of the adrenal and pelvic regions may be warranted Unless a demonstrable tumor exists, removal of an ovary does not appear wise Since the more common situation is that of slowly developing maturity without evidence of a tumor, the usual therapy is not curative but palliative Irradiation of the pituitary or gonads should not be used since the results, if significant, would be permanent reduction of later normal functions It is

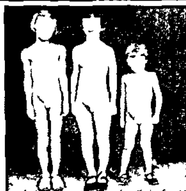


Fig 37 (upper left) —Precocious development Age 5 Breasts began to enlarge about age 3 after scarlet fever Pubic hair appeared at 3½ years From 5 to 8 patient grew 7 in gained 27 lb finished third grade and was well and properly adjusted socially

Fig 38 (upper right) —Note increasing adult feminine type of body proportions At 8½ epiphyses were closing and bone age was 15-16 year type No evidences of intracranial lesion or other abnormality

Fig 39 (below) —Patient at age 5 with normal girl her age at her

suggested that the one valuable feature of treating precociously adolescent children would be to help them attain reasonably normal stature Owing to the premature sex hormone production, epiphyseal clo sures occur at an early age, thereby limiting growth of long bones and leaving the individual a dwarf This seems paradoxical, in view of the fact that the child is tall for his age during the early years The fact that stature less than 5 ft is ultimately attained by such children should be accepted as a basis for the intensive use of growth promoting pituitary extracts before the epiphyses unite There is a possibility, not yet demonstrated, that such growth promoting extracts may tend to retard the activity of the sex-stim ulating factors This would be entirely desirable in these cases

The physician must advise the parents in the edu cation, emotional guidance and social supervision of such children Adolescent adjustments are enough of a problem for the normal child The detailed needs of precocious children must be anticipated so far as possible to avoid psychic difficulties Cooperation of teachers is likewise essential

DELAYED ADOLESCENCE

The converse situation of retarded puberal changes is a far commoner clinical problem The normal range of onset of adolescent changes is difficult to state The menarche in the United States is said to occur between 12 and 15 years most frequently about

14 Variations as far as 11 to 16 years are not infrequent There are *no equally obvious objective phenomena* which can be dated in the maturation of boys In both sexes the changes in bodily proportion, development of external genitalia, alteration of hair pattern and appearance of new types of behavior are often the signals which inform the parents and the family doctor of the beginning of adolescence The process is one of several years during which the final increment of stature is added, epiphyses are closed, skeletal type is fixed and the gonads increase their activity to a level consistent with fertility These *varied aspects of the metamorphosis from childhood* into adult life depend on numerous factors genetic and nutritional as well as endocrine Among the endocrine factors pituitary, thyroid and gonad responsibilities are most evident Unless hypothyroidism can be demonstrated by definitely low basal metabolic rate abnormally high blood cholesterol content and significant retardation in bone age, the therapeutic use of thyroid is not advised Since the use of gonad hormones will not stimulate the gonads, it is unwise to try to influence delayed development with testicular or ovarian *hormones By exclusion* the therapeutic problem, if endocrine is to be considered one of pituitary hypofunction If the growth rate is adequate the only pituitary function which is subnormal is the gonadotrophic

Obesity may complicate the picture of delayed adolescence or infantilism in which case the mixed syndrome of adiposogenital dystrophy or Froehlich syn

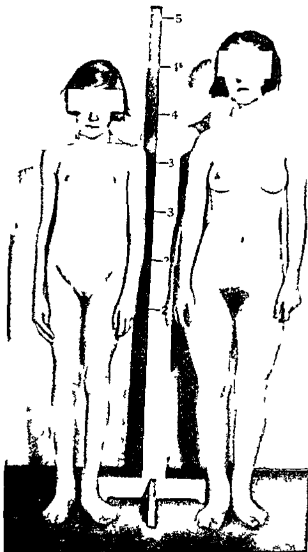


Fig 40—Same patient as preceding at age 9 beside normal girl of same age Menses regular for 1 year Epiphyses closed Bone age 19 years Height at age 10 was 58 inches

portance lies in their being understood sufficiently to receive skilful neglect

In girls, there may be several presenting symptoms Primary amenorrhea or failure of menses to appear by the normal time, should not be diagnosed until after age 15 at the earliest Absence of other changes which precede the approaching menarche by one to three years serves to make such a diagnosis more secure In recent years attention has been directed to a curious syndrome marked by primary amenorrhea and stature reaching approximately 56 in which may or may not be complicated by obesity (see Fig 44 p 226) In some of these dwarfed and infantile girls there is no evidence of any ovarian function The fundamental etiology of this syndrome is unknown Such patients ought to receive intensive study

If menstrual flows have appeared but infrequently and at irregular intervals a period of a year or more should be allowed to elapse to determine whether increasing regularity of interval will not occur spontaneously If there is no improvement, treatment may be begun When the complaint is of scanty flow with regular rhythm there is no urgency about therapy unless there are other evidences of inadequate development or in later years unless fertility is demonstrably reduced The far more common problem is that of menorrhagia whether the intervals are regular or unpredictable Treatment is more necessary for this than for any other condition caused by underactive ovaries Unless local pelvic lesions or bleeding tendency can be found menorrhagia is usually the

drome, is diagnosed Obesity is to be treated, as always, by dietary procedures outlined in Chapter 14 Occasionally the relief of obesity is itself a factor in causing improvement in gonad function and should be attempted in all patients who come under clinical care in the earlier years of the second decade Again it is emphasized that such obesity should be treated without use of thyroid unless there are clear evidences of hypothyroidism Obesity is not in itself good evidence of reduced thyroid function Of especial importance in reducing the weight of children is provision for adequate supplies of vitamins and of protein The fat-soluble vitamins are often taken in suboptimal amounts, owing to rigid restriction of food fats for reducing weight Concentrates of vitamins A and D must then be given regularly

When clinical judgment indicates that significant delay in sexual development of a boy merits treatment, the program should be based on daily injection of small doses of pituitary or pregnant mare's serum extracts These substances act quickly, for brief periods of hours after each administration, and must therefore be given frequently Details about the standardized extracts and the rationale of the therapy will be found in Chapter 12

Attention is sometimes drawn to slightly tender masses in the mammary region of boys entering the adolescent period Such "subareolar nodes" must not be interpreted as evidences of pathologic processes, for they occur in many boys and are temporary evidence of changing hormone balance Their only clinical im-

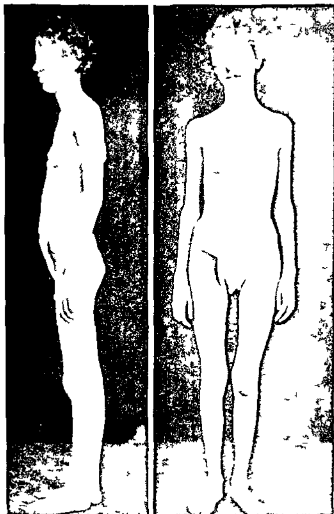


Fig 41 —Adolescent hypopituitarism

consequence of reduced intensity of ovarian secretion This may involve low production of estrogen, erratic cycles of estrogen secretion or failure of ovulation and progesterone secretion by the corpus luteum, with or without the presence of follicle cysts in the ovaries The first requisite is to be certain that marked anemia has not occurred If it has, curettage may be required, with transfusions to restore a safe concentration of red cells If anemia is not marked, the diagnostic studies may be undertaken deliberately The problem is discussed in detail in Chapter 11 Traditionally these patients have been given thyroid, and some have shown striking improvement It is usually possible to detect the thyroid deficient cases by use of basal metab olism tests and blood cholesterol estimations Successes with thyroid in other cases are rare On the other hand, the use of gonadotrophic pituitary extracts to stimulate ovarian secretion has produced satisfactory results in juvenile menorrhagia Such therapy should be administered in cycles of injections over periods not exceeding two weeks each month or each menstrual cycle, as explained in Chapter 11

JUVENILE DIABETES MELLITUS

The important features of diabetes mellitus in the first two decades as distinct from the disease in the adult, are sudden onset variability of dietary and insulin prescriptions which must be used and the special problems of dwarfism or increased stature In other respects the diagnostic and therapeutic procedures

are the same as those outlined in Chapter 9 The onset is frequently so sudden, with marked ketosis and danger of coma, that intensive treatment may be required at the time of the first diagnostic examination This sudden onset indicates congenital or hereditary deficiency in the islands of Langerhans plus extensive toxic effects of an acute infection Recent acute infectious disease is a common precursor of diabetes in children If there is a familial history of diabetes, a diligent search should be made for diabetes among all siblings Following such acute onset the sugar tolerance is often improved after a few weeks or months of careful management of the diabetes, but later exacerbations must be expected in most cases This fluctuating tolerance makes continued clinical supervision more important than in diabetics in the latter half of life

Further aspects of the lability of juvenile diabetes are the rapid changes which follow intercurrent infections sometimes requiring changes in insulin dosage This cannot be predicted, and hence every diabetic child must be watched vigilantly through the course of any febrile illness The vigorous and highly variable exercise characteristic of children contributes another important factor in management The insulin dosage should be set to fit the typical day of the child s routine When a day of relative inactivity occurs there is often glycosuria but this should be ignored On the other hand, if activity is suddenly increased over the usual amount, the exercise may serve to deplete the sugar supply from diet and glyco

olism test is seldom dependable, and diagnosis must be verified by use of the bone age determinations and blood cholesterol estimations, as discussed in Chapter 5 Thyroid dosage should be kept at the maximum which will not cause tachycardia, sweating or nervous disturbances Progress in school improvement of appearance of the skin and development of osseous structures are the best guides to adequate dosage until dependable basal metabolism tests can be used

Hyperthyroidism rarely occurs before adolescence In the first two decades it is safe to use medical management of thyrotoxic children who can be supervised Psychic and emotional disturbances are to be minimized Remissions may be induced with iodine some times this state can be maintained by use of small doses of iodine regularly Spontaneous remissions are not uncommon Use of x ray therapy rather than surgery is worth consideration For patients with severe thyrotoxicosis with loss of weight persistent disturbance of heart action and no adequate remissions under management the only recourse may be the conventional subtotal thyroidectomy

For prophylaxis of all types of goiter, the most significant step is the universal use of iodized salt in areas where goiter is common This is especially important for children The amounts of iodine included in the diets of even small children in homes using only iodized salt are adequate for prophylaxis so far as can be determined at present Daily average intake of 50 micrograms (0 05 mg) is adequate to prevent goiter at any age If there is any doubt about the

gen stores, as a consequence of which an insulin reaction occurs within the following 24 hours This reaction seldom occurs during the exercise, and with the use of protamine zinc insulin it commonly appears during the night after the unwonted exertion The child should be fed moderate additional amounts of foods such as milk, bread or fruit shortly after such bouts of exercise Occasional glycosuria is far less dangerous than repeated insulin reactions

When a diabetic child is shorter than usual for his age, he should be considered a candidate for treatment with pituitary growth-promoting extract Of course his diet must be adequate in calories and protein, but this can be gaged by his ability to gain weight If growth does not follow at a normal rate, he may be treated with pituitary extracts, as explained in Chapter 4 There is no basis in clinical experience for the fear that this will make the diabetes more severe The typical diabetic child is tall for his age, but he does not show precocious puberty This precocious growth in stature has led to a suspicion that there is a pituitary factor in the etiology of the diabetes Further evidence of this is not available Such tall diabetic children need merely to have adequate food to maintain an optimum weight for height

THYROID DISORDERS IN CHILDREN

Hypothyroidism may appear as cretinism or as myxedema beginning in early childhood Both types deserve early, intensive and persistent treatment with thyroid Before puberty the use of the basal metab-

olism test is seldom dependable, and diagnosis must be verified by use of the bone age determinations and blood cholesterol estimations, as discussed in Chapter 5 Thyroid dosage should be kept at the maximum which will not cause tachycardia sweating or nervous disturbances Progress in school, improvement of appearance of the skin and development of osseous structures are the best guides to adequate dosage until dependable basal metabolism tests can be used

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adequacy of iodine intake, this may be augmented by the prescription of weekly doses of 10 mg in any one of a number of special tablets made for the purpose The use of plain sodium iodide is equally good There is no reason to fear unfavorable results from the use of iodized salt or weekly doses of iodized oils in tablet form, or even simultaneous use of both This same therapeutic material is to be employed in the treatment of nontoxic enlargement of the thyroid as seen in the first two decades Unless such goiters have been caused to regress before the age of 20, iodine therapy seldom achieves much

TEMPORARY OBESITY IN CHILDREN

The occurrence of obesity in children and early adolescents is frequently followed by loss of excess weight without sustained dietary precaution Therefore many parents and physicians condone obesity at this age or even refuse to attempt any dietary restrictions However, some of these fat children do not lose weight later but become increasingly addicted to eating habits which make later reduction more difficult There is no known way to distinguish the children who will later attain an ordinary weight Consequently it seems wise to exercise the same dietary caution in all obese children that would be necessary for known persistent obesity at any age The chief problem involved is that of securing the willing cooperation of the child The technical diagnostic problems and construction of the diets are dealt with in Chapter 14

Chapter 14

OBESITY

A *definition* of obesity is an excess of fat over the normal expected for the height, age and sex of the patient Obviously this definition presupposes a knowledge of optimum weights Medical men can turn for this knowledge to two types of standards tables of weight for height, or clinical impressions based on experience and judgment Each standard has its value in clinical diagnosis Their limitations should be recognized Tables of weight have been compiled chiefly by life insurance students, whose ob jective has been consideration in terms of longevity In the earlier efforts, no attention was paid to the slowly accumulating disadvantages of obesity The later experience of insurance companies has tended to lead to downward revision of the weights in the dec ades after 30 In other words there is reason to believe that it is unwise to allow much addition of weight after this age Furthermore, all such tables are statistical statements of what a theoretical person a 'normal individual, weighs For any one height, age and sex such a figure as shown in the tables represents an average of the weights of a number of individuals who differ from each other Those who are familiar with the statistical studies on which these

adequacy of iodine intake, this may be augmented by the prescription of weekly doses of 10 mg, in any one of a number of special tablets made for the purpose The use of plain sodium iodide is equally good There is no reason to fear unfavorable results from the use of iodized salt or weekly doses of iodized oils in tablet form, or even simultaneous use of both This same therapeutic material is to be employed in the treatment of nontoxic enlargement of the thyroid as seen in the first two decades Unless such goiters have been caused to regress before the age of 20, iodine therapy seldom achieves much

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TABLE 4 (CONT)

WEIGHTS OF GIRLS AND WOMEN IN POUNDS

HEIGHT IN	AGE YR.									
	12	13	14	15	16	17	18 19	20	30	50
71					139	142	146	150	158	174
70					136	139	142	145	154	169
69				131	132	135	138	142	150	165
68			125	127	128	132	135	138	146	160
67	107	114	120	123	124	128	132	134	142	155
66	104	110	116	119	121	125	129	131	138	151
65	100	106	112	115	118	122	126	127	134	147
64	97	102	108	111	114	119	122	124	131	143
63	93	99	104	107	111	116	119	121	128	139
62	90	95	100	104	108	112	117	118	124	135
61	87	92	96	100	105	110	114	115	121	131
60	84	88	92	97	102	107	111	112	118	128
59	81	85	89	93	99	104	108	110	116	125
58	78	82	85	90	96	101	105	107	113	122
57	75	78	82	87	93	99	103	105	111	119
56	72	75	78	84	90	96	100	102	109	117
55	70	72	75	81	87	94	98	100	107	114
54	67	69	72	78	84	91				
53	64	66	69	75	82					
52	61	63	66	72	79					
51	59	61	63	69	77					

the figures given in a table to a particular patient It is often easier for an experienced physician to pass judgment on weight optimum from examination of the nude patient without the tables But these tables are of help in making diagnoses definite and in checking what may otherwise be an esthetic judgment rather than one based on prognosis for health Fortunately the trend in esthetic standards of bodily proportion in American life is toward the avoidance of obesity but also more recently to well nourished bodies rather than to the sylphlike lines of the earlier part of the Twentieth Century The clinician should recognize the assistance of these popular standards for they fur

TABLE 4

WEIGHTS OF BOYS AND MEN IN POUNDS

HEIGHT IN	AGE YR.									
	13	14	15	16	17	18	20	30	40	50
76						169	179	193	201	206
75				158	161	164	174	187	195	200
74			153	154	156	160	169	181	189	193
73			148	149	152	155	165	175	183	187
72		140	142	144	147	151	160	170	178	181
71		135	138	140	143	147	156	165	172	176
70		131	134	135	139	142	151	160	167	170
69	119	126	129	131	135	138	147	155	162	165
68	115	122	125	127	131	134	143	150	157	160
67	111	118	120	123	127	130	138	146	152	155
66	107	114	116	119	123	127	135	141	147	150
65	103	109	112	115	119	123	131	137	143	146
64	100	105	109	112	115	119	127	133	138	141
63	96	102	105	107	112	116	124	129	134	137
62	93	98	101	103	108	112	120	126	131	133
61	90	94	97	100	104	109	116	123	127	129
60	86	90	94	96	101	105	113	119	124	126
59	83	86	90	93						
58	80	83	87							
57	78	80	83							
56	74	77								
55	71	73								

tables are based know that it is unsafe to expect such figures to be absolutely accurate An allowance of 10 per cent variation above and below the average is always to be made Thus for a weight of 120 lb in such a table, the normal individuals would be found within 10 per cent, or 12 lb, of this weight, i e, from 108 to 132 lb Of course this is not to suggest that a person who is well proportioned at 108 lb would be equally normal at 132 It means that owing to the variety of diameters of chest and pelvis of breadth of shoulders and of type of bones, the clinician must use his judgment to the extent of at least plus or minus 10 per cent in deciding how rigorously he can apply

disorder The question cannot be answered with desirable precision Illustrations of the clinical types involved will help to clarify the problems mentioned

TABLE 5

HEIGHT—WEIGHT—AGE TABLE FOR CHILDREN

TYPICAL AGE YR.		HEIGHT IN	TYPICAL NUDE WT LBS	
BOYS	GIRLS		BOYS	GIRLS
14		60	90.3	91.2
	13¼	59	85 9	85.7
13¼		58	81 0	80.8
		57	76 6	76 1
12¼	12	56	72.5	72 0
		55	68 9	68.2
11¼	11¼	54	65 4	64.7
		53	62.2	61.6
10	10¼	52	59.5	58.6
		51	56.8	56 0
9	9¼	50	54 4	53.5
		49	52.0	51.2
8	8¼	48	49 9	49 1
		47	47 9	47 0
7	7¼	46	46 0	45 0
		45	44.2	43.5
6	6¼	44	42.5	41.7
		43	40 9	40 1
5	5¼	42	39.3	38.5
4½		41	37.8	36 9
		40	36.3	35.5
	4	39	34 8	34 0
3½		38	33.3	32 6
		37	31 9	31.2
	3	36	30 5	29.8
2½		35	29 0	28 4
		34	27 6	27 0
2	2	33	26.2	25.7

Orthopedic problems of various types lead to such enforced inactivity that a gain in weight is often the consequence unless the food intake is curtailed There is, of course, no endocrine problem in such an instance Figure 42 illustrating an "orthopedic type" of obesity shows the rather generalized distribution

nish some of the more powerful types of impetus to adhering to a reducing regime

Some of the simplest useful tables of weights were prepared by Dr C R Bardeen over 30 years ago, based on extensive measurements of a large number of healthy Wisconsin residents They are reproduced (Table 4, pp 222-223) in abbreviated form adequate for clinical reference These are nude weights An allowance ot 2 to 3 lb is made for women's clothing, 6 to 8 lb for men's

In height-weight-age tables for children, both age and weight are referred to height In Table 5, on the left are given the typical ages at which boys and girls were found to have attained a given height and on the right are given the weights that were found typical for a given height When weight is taken in street clothes, estimation of their weight must be made and subtracted from the total to obtain the nude weight

Since we know that the laws of the conservation of matter and of energy apply to the human body, it will be obvious that obesity must result from too much food in proportion to the output of energy This broad generalization applies to all types of obesity regardless of etiology Aside from sheer overeating unwise eating of high calory diets and lack of physical activity, there are a number of clinical conditions which are accompanied by obesity This has led to the supposition that there is a peculiar way in which some of these conditions cause the excessive weight Most of these states are in some way caused by endocrine disturbances Is obesity in such cases an endocrine

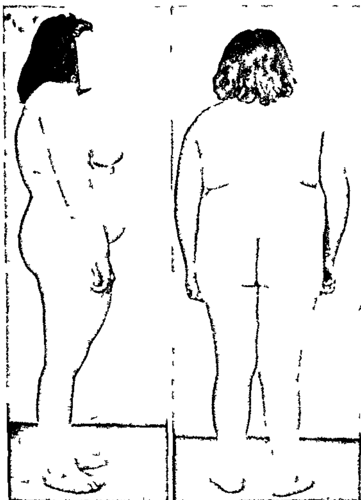


Fig 42 — Orthopedic type of obesity Age 13 60 in tall 187 lb Gain of 32 lb without growth in the last year was the most rapid advance though obesity had been pre ent three years Child had been plump before but obesity became serious after deforming osteomye litis in the heel which limited exercise Menarche at 2 with regular menses No evidence of thyroid di ease

of excess fat throughout the body The necessity for reduction with strict diet because of the limited possibility for exercise is apparent This is often important to allow orthopedic procedures to achieve the desired results

Hypoglycemia may be a cause of obesity, as illustrated by the photographs of a woman who had tried, with some medical help, but in vain, to reduce her enormous weight (Fig 19) History and examination showed no adequate cause for the obesity, save admitted marked hunger between meals The conventional sugar tolerance test showed blood sugar values distinctly lower three hours after the ingestion of 50 Gm dextrose than before eating This low blood sugar concentration coincided with the hunger which characteristically occurred between meals, leading to lunching which was too frequently of high calory foods It is questionable whether the long standing mild symptoms in such a clinical case are to be referred to excessive production of insulin (an endocrine problem) or merely to such rapid storage of sugar after meals that blood sugar was temporarily depleted Treatment of such obesity of course involves limitation of calories, but with attention to the limitation of the amount of sweet foods at any time and possible use of simple fruits to relieve the hypoglycemic hunger between meals The use of the higher fat diets mentioned in Chapter 7 for treatment of severe hypoglycemia may be the most comfortable and successful way to manage some such obese patients This hypoglycemic background for obesity

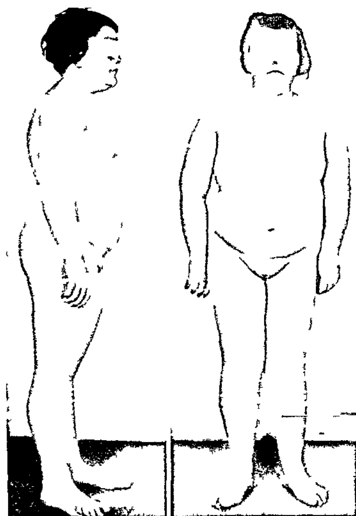


Fig 44—Froehlich syndrome with dwarfism Sella turcica very small Epiphyses closed in spite of primary amenorrhea

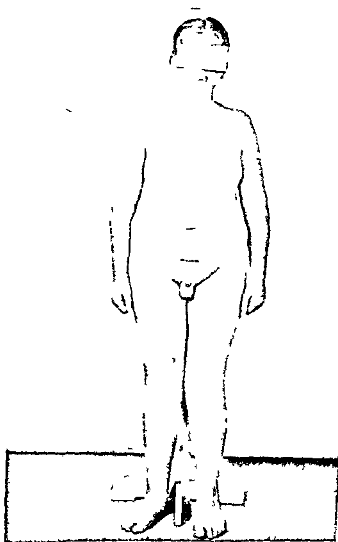


Fig 43—Froehlich syndrome age 14 Prompt reduction on 1 200 calory diet following failure to reduce on thyroid Development of genitalia and broadening of shoulder girdle followed use of pituitary gonadotrophic extract (Preh in)

should be suspected from a history of marked hunger between meals and should be confirmed by blood sugar determinations at the hunger periods or by sugar tolerance tests The condition is much commoner in children than adults In childhood it appears to be an exaggeration of the normal physiologic hunger mechanism.

Hypothyroidism is a factor in obesity of moderate amount not only in cretinism (Fig 13 facing p 78) and myxedema but in the milder cases more frequently seen Although this is not a common cause of obesity it is important that the clinician look for the characteristic diagnostic signs of skin pulse reflex, mental and menstrual phenomena and that he confirm the diagnostic decision by estimations of basal metabolism blood cholesterol and bone age (in children) when there is any doubt

Pituitary participation in causing obesity has been debated and continues to be a source of much misunderstanding The commonest type is the *Froehlich syndrome* or *adiposogenital dystrophy* Here there is no doubt that pituitary underactivity is the background for the failure of the gonads to develop and function Such a condition is illustrated by the boy shown in Figure 43 The obesity was brought under control by dietary means A previous trial of thyroid had been disappointing The development of genitalia and of secondary sex characteristics followed promptly the use of pituitary therapy (Prephysin)

A further example of pituitary obesity is shown in Figure 44 (facing p 228) a young woman, aged 19,

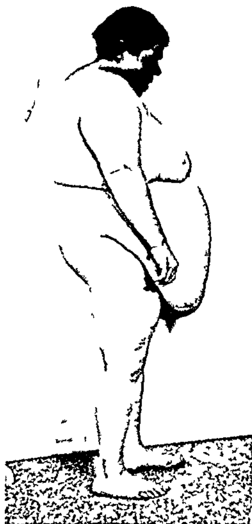


Fig 45.—Postpartum adiposogenital dystrophy

form by the case of a woman shown in Figure 45 who became excessively fat only after a pregnancy Evidence of hypopituitarism occurred at the same period, shown by irregularities of menstrual cycles and loss of fertility The condition is essentially identical with the Froehlich syndrome, but had its origin after some disturbance during the pregnancy Such cases are all too common Of course it is known that there are anatomic and physiologic changes in the anterior pituitary during pregnancy usually only temporary but sometimes permanent as in this case, and in those women who develop acromegalic appearances during pregnancy The assumption of pituitary responsibility for the obesity is made less plausible, however, by the common history of obesity after pregnancy without any evidences of disturbed pituitary function so far as control of growth factors or gonad stimulating hormones is concerned Yet many women who have had no problem in weight control before pregnancy find obesity a persistent annoyance ever after This may occur after a first or any subsequent pregnancy but it is still not the usual result of pregnancy This clinical connection makes it seem certain that some metabolic fault has been occasioned by the pregnancy which leads to obesity The details are cited to show how easy it is to assume that the pituitary is responsible whereas pathologic studies and animal experiments point to another cause

Studies on rats and dogs are particularly conclusive in demonstrating that there is an area in the hypothalamic region of the brain just above and posterior

of superior intelligence but retarded growth, with primary amenorrhea, lack of secondary sex characters and obesity The skeletal dwarfism shows still further the pituitary underactivity An x-ray showed a small sella turcica Although closure of epiphyses was not quite complete at 19, growth promoting extracts have not accomplished any growth Basal metabolism test, blood cholesterol concentration and delicate skin texture, as well as mental development, all demonstrate that this is not a case of thyroid deficit

If all patients with underactivity of the anterior pituitary had this combination of obesity with the other functional deficits, pituitary responsibility for the obesity would be easy to believe But there are likewise many patients who have subnormal gonad activity which can be attributed to the anterior pituitary or dwarfism due to hypopituitarism, yet are not obese Such a condition is illustrated in Figure 41 This young woman had irregular and excessively long menstrual flows, associated with demonstrably low activity of the ovaries This probably indicates that her anterior pituitary was underactive It was not possible for her to achieve even a normal weight for her height The increasing recognition not only of Simmonds' cachexia but of minor degrees of pituitary underactivity with asthenic states as well as genital disorders is further illustration of the failure of all hypopituitarism to lead to obesity The Lorain type of dwarfism (Figs 5 9, pp 58-59) is one of the best examples of hypopituitarism without obese tendency

This puzzling situation is illustrated in another

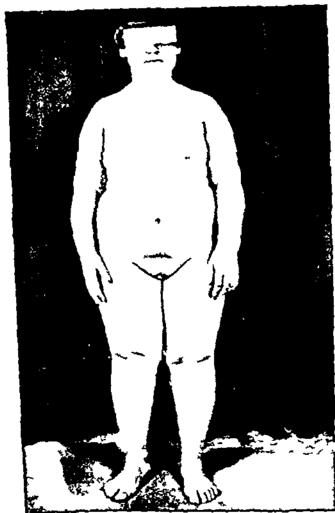


Fig 46 —Postencephalitic obesity

to the pituitary which is intimately related to weight control Destruction of this region leads to obesity, with no alterations in bone growth or gonad activity unless there has been simultaneous pituitary destruction It is still undetermined whether this weight control is exerted by an endocrine mechanism But there is an increasing body of clinical cases in which the history and examination indicate lesions in this region leading to obesity, often without disturbance of pituitary function Apparently, encephalitis is particularly prone to leave permanent effects in the hypothalamic area, sometimes producing obesity, again disturbing the centers from which impulses pass to the autonomic system or the centers leading to the posterior portion of the pituitary gland Figure 46 shows an obese girl without evidences of the Froehlich syndrome, whose difficulty began after encephalitis, which also left some disturbances of cerebral cortical function

Figure 1 illustrates the case of a woman whose obesity is associated with diabetes insipidus The lesion is believed to be hypothalamic, with secondary effects in the posterior pituitary leading to the diabetes insipidus As a consequence of these considerations, it is increasingly probable that obesity is not a pituitary problem but a condition due to lesions or disturbances of some center in the hypothalamus Obesity associated with pituitary regional disease is spoken of as *hypothalamic obesity* Its treatment is peculiarly fraught with difficulty because of lifelong necessity for the strictest of diets to attain control

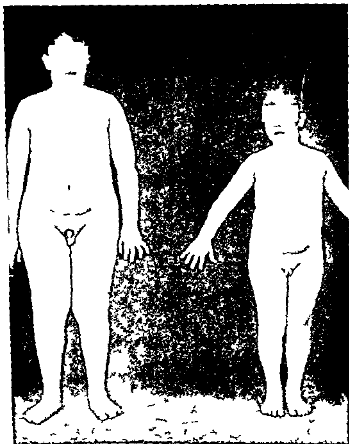


Fig 48 —Laurence Moon Biedl syndrome in brothers

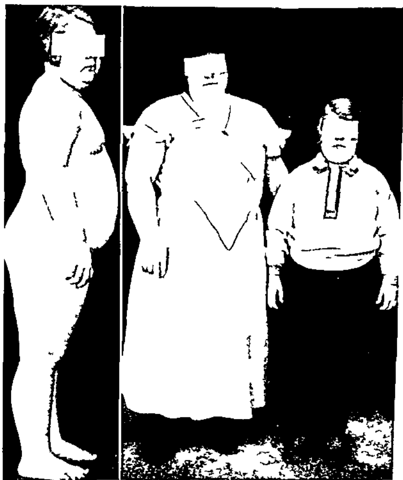


Fig 47 —Familial obesity

These patients also are among those who find loss of weight very slow on careful dieting Such obesity following pregnancy is probably to be attributed to small lesions owing to infarction, as described by Sheehan (See Chapter 11)

Familial obesity is clinically recognized by obvious means The mechanism causing the weight abnormality is not evident It cannot well be the same as that of the Froehlich syndrome because of the low fertility in the latter case But it is entirely possible that familial hypothalamic patterns may exist Figure 47 shows an obese girl whose general appearance would be consistent with a Froehlich syndrome but whose picture with her mother leaves no doubt of the familial nature of the trouble The tendency may be transmitted through either sex Success in reducing the daughter cannot be expected unless the mother is willing to follow similar dietary limitations

A curious familial form of obesity is the rare anomaly known as the *Laurence Moon Biedl syndrome* Here the additional features are low mentality polydactylism, retinal atrophy with or without excessive pigment deposition, poor genital development and marked tendency of the entire syndrome to occur in siblings but not in other generations There is no conclusive evidence that this is an endocrine picture It may be a genetic curiosity It is important that it be recognized in order that an accurate and guarded prognosis be given Figures 48 and 49 show pictures of brothers with this difficulty, in whom the extra toes and obesity are evident Visual as well as mental



Fig 49—Same cases as in Figure 48

of the body cells They provide the material for the replacement of the wear and tear on body cells which is going on continuously, entirely independent of work. The digestive and other enzymes and such hormones as thyroxine, insulin and adrenalin are so closely re lated to the amino acids, of which proteins are made up that these internal secretions could only be made by the body from protein Obviously then, it is not permissible to place an individual on a diet which will fail to yield adequate amounts of protein for these needs Large amounts of protein are not necessary especially for adults One hundred grams daily of good quality protein is undoubtedly in excess of the requirements of any adult Any excess protein is used by the body as so much carbohydrate and fat namely, as a source of energy It is both financially and physio logically expensive, hence to be avoided save as one indulges in the foods one likes best

If meat, milk and eggs are too greatly restricted the diet may become deficient in vitamins for meat and milk provide large fractions of the usual dietary intake of the B group, and milk and eggs furnish much of the usual intake of A and D Reducing diets often require additional sources of vitamins A and D for this reason.

Carbohydrates and fats are used by the body as sources of energy and the excess is stored as fat for later use or as a mechanical protection against injury and cold The carbohydrates form the main part of the energy-yielding food for many people hence the injunction to cut the starches if weight reduction is

handicap interfered with school and play No therapy has been found helpful for the condition, save dietary control of the obesity

Another striking form of obesity is part of the *Cushing syndrome*, which probably has some pituitary disturbance in all cases, frequently with lesions in adrenal cortex, ovary or thymus as well The peculiarities of hair distribution, hypertension, changes in sex factors and the purplish striations on the torso call attention to the nature of this condition (Fig 28 facing p 168) In this connection, mention must be made of the far more frequent cases of obesity, increased facial and body hair and slight disturbances of the reproductive system in women There is too little evidence to classify them as examples of the Cushing syndrome, and the mechanism involved in the hirsutism remains unexplained No helpful treatment has been found

Therapy

All fat people are fat because they have eaten more food than their bodies needed This statement seems dogmatic, but it must apply if the laws of the conservation of energy and matter are true There is no denying that some fat people eat little and that some lean people are voracious To gain an understanding of the matter, one must examine the chief sources of energy for the body and the principal avenues for the expenditure of energy by the body The proteins are essential to life for at least three reasons They provide the material for the growth of the protoplasm

PROTEIN 50 GM CARBOHYDRATE 126 GM FAT 55 GM CALORIES 1,200

STANDARD

Breakfast

Fruit	1 portion
Bread	1 slice
or	
Cooked cereal	¾ cup
Sugar	1 teaspoon
Butter	1 pat
Egg	1
Milk (whole)	½ cup

Dinner

Lean meat	1 small serving
Potato	1 portion
Vegetables	3 portions
Bread	1 slice
Butter	1 pat
Fruit	1 portion

Supper

Lean meat	1 small serving
Vegetables	3 portions
Bread	1 slice
Butter	1 pat
Fruit	1 portion
Milk (whole)	½ cup

LOW COST DIET

Breakfast

Bread	1 slice
or	
Cooked cereal	¾ cup
Sugar	1 teaspoon
Butter	1 pat
Egg	1
Milk (whole)	½ cup

Dinner

Lean meat	1 average serving
Potatoes	2 portions
Vegetables	3 portions
Bread	1 slice
Butter	1 pat

Supper

Potato	2 portions
Vegetables	3 portions
Bread	1 slice
Butter	1 pat
Milk (whole)	1 cup

PROTEIN 50 GM CARBOHYDRATE 70 GM FAT 50 GM CALORIES 930

Breakfast

Fruit	1 portion
Egg	1
Bread	½ average slice
Butter	1 pat
Skim milk	½ cup

Lunch

Lean meat	1 small serving
Vegetables	2 portions
Bread	½ average slice
Butter	½ pat
Fruit	½ portion
Skim milk	½ cup

Dinner

Lean meat	1 small serving
Vegetables	2 portions
Bread	½ average slice
Butter	½ pat
Fruit	1 portion
Skim milk	1 cup

PROTEIN 75 GM CARBOHYDRATE 136 GM FAT 73 GM CALORIES 1 500

Breakfast

Fruit	1 portion
Bread	1 slice
or	
Cooked cereal	¾ cup
Butter	1 pat
Egg	1
Milk (whole)	½ cup
Sugar	1 teaspoon

Dinner

Lean meat	1 average serving
Potato	1 portion
Vegetables	3 portions
Bread	1 slice
Butter	1 pat
Fruit	1 portion
Milk (whole)	1 cup

Supper

Lean meat	1 average serving
Vegetables	3 portions
Bread	1 slice
Butter	1 pat
Fruit	1 portion
Milk (whole)	½ cup

desired However, it is possible with perfect safety and palatability to have the fat furnish as much as 75 per cent of the total energy in the diet of an individual doing ordinary work Greater amounts of fat than this are seldom justified because of the inability of the body to oxidize fat completely if it is given in too large an amount per day When fat is burned incompletely, the acetone bodies accumulate and appear in blood and urine, a condition called "ketosis" The ketosis may lead to acidosis if it is severe enough and long enough continued The process is the same, whether it occurs in fasting, fevers or diabetes In the first two conditions there is a lack of carbohydrate due to lowered intake In diabetes there is inability to burn carbohydrate in adequate amounts even though it be present

REDUCING DIETS

The essence of the wise reducing diet is that ordinary amounts of protein are used but the fat of the diet is greatly reduced The carbohydrate intake is maintained at a level well above that which will prevent ketosis The total food intake in terms of calories is well below the expenditure of energy Under these conditions, body fat is drawn on as an important source of energy, and excess weight is used up It makes little, if any, difference whether the body oxidizes food fat or body fat save in the matter of weight

The other half of the picture is the group of body functions which expend energy and therefore use up

CHEESE PORTIONS	
American cheese	2 oz
Cottage cheese dry	½ cup
Cream cheese	2 oz

POTATO

1 portion of potato is ½ small potato a piece the size of a small egg — substitutes may be

Red kidney beans	¼ cup
Corn canned	3 tbsp
Fresh limas	½ cup
Boiled rice	½ cup

MEAT

1 small portion of meat weighing 2 oz or the size of an egg may be replaced by

1 average serving of fish or chicken or 1 portion of cheese or 2 eggs

1 average portion of meat weighing 3 oz or the size of 1½ egg may be replaced by

1 large serving of fish or chicken or 2 portions of cheese or 3 eggs

foods There are three of major importance First is the basal metabolism This includes the work done in breathing and in circulating the blood when the body is at rest It embraces all those processes which make up the continuous life of the body cells and which keep the body warm under ordinary conditions The tonus of muscles is in this latter category This basal metabolism is constant in the same sense that temperature and pulse rate are constant It is under the regulation of the internal secretion of the thyroid gland A second outlet for energy is the stimulation of heat production by foods, called specific dynamic action This usually amounts to not more than 10 per cent of the basal metabolism To increase this heat loss one must increase the food The means would therefore defeat the purpose The third outlet for energy is physical exercise The actual energy loss may easily go to twice the basal metabolism by exercise that is not beyond anyone It may be only 20 per cent more than the basal metabolism The variability of this factor is of great importance for reduc

FOOD PORTIONS TO ACCOMPANY REDUCING DIETS

Vegetable Portions

Asparagus cooked	14—3 tips or ½ cup	Onions, raw	¾ cup
Asparagus fresh	8—6 stalks	Onions raw—green stick	12—4
Beets diced	¼ cup	Oyster plant	2 tbsp
Beet greens	½ cup	Parsnips, boiled	2 tbsp
Broccoli	½ cup	Peas fresh	2 tbsp
Brussels sprouts	⅙ cup	Peas, canned	3½ tbsp
Cabbage, cooked	½ cup	Radishes	12 medium
Cabbage raw	⅔ cup	Rhubarb	⅔ cup
Carrots	¼ cup	Romaine	10 leaves
Cauliflower	⅔ cup	Rutabaga	2 tbsp
Celery raw	5—7 stalks	Sauerkraut	⅔ cup
Celery cooked	⅔ cup	Sauerkraut juice	½ cup
Celery cabbage cooked	⅔ cup	Spinach	½ cup
Celery cabbage raw	1 cup	String beans fresh	¼ cup
Cucumber diced	⅔ cup	String beans canned	½ cup
Dandelion greens	½ cup	Swiss chard	⅔ cup
Eggplant	½ cup	Squash Hubbard, mashed	⅓ cup
Kohl rabi	⅙ cup	Squash summer mashed	⅔ cup
Lettuce	¼ sm. head	Tomatoes, cooked	½ cup
Green limas canned	3 tbsp	Tomatoes fresh	1 small
Mushrooms	as desired	Tomato juice	½ cup
Okra, fresh	¼ cup	Turnips	3 tbsp
Okra canned	½ cup	Watercress	2 cups
Onions cooked	½ cup		

Fruit Portions

Apple raw	⅔ sm. apple	Oranges	1 small
Applesauce	½ cup	Orange juice	1/ glass
Apricots	4 halves	Peach fresh	½ medium
Banana	⅓ medium	Peach canned— halves	2 halves
Blackberries fresh	¾ cup	sliced	⅓ cup
Blackberries canned	¾ cup	Pears, fresh	½ pear
Blueberries fresh	1/ cup	Pears, canned	2 halves
Blueberries canned	⅓ cup	Pineapple fresh or canned diced	½ cup
Cherries red pitted canned	½ cup	sliced	1¼ slices
Cherries, Royal Ann	18 cherries	Plums, fresh or canned	3 plums
Cherries fresh red	½ cup	Prunes fresh or canned	3 prunes
Cherries *fresh black*	⅓ *cup*	Raspberries fresh	1 cup
Gooseberries	⅔ cup	Raspberries canned	½ cup
Grapefruit fresh	½ med. or 6 sections	Strawberries fresh	1¼ cup
Grapefruit, canned	6 sections	Strawberries canned	1⅓ cup
Grapes fresh	10 grapes	Tangerines	2 medium
Loganberries, fresh	⅔ cup		
Loganberries, canned	1 cup		
Melon cubed	1 cup		

ful The reducing diets given here include some of the menus of the type used for these problems It will be noted that variety is easily achieved and that no weighing of foods is necessary

Patients should be warned that weight reduction does not always proceed at a steady pace Sometimes as fat is consumed from the body stores, water is stored in approximately equal amounts If a daily weight chart is kept, no loss may be seen for as much as two weeks But ultimately the loss of water will follow, and weight loss will be as demanded by the laws of conservation of matter and energy It is wise to explain this to patients and also to caution against daily weighing lest discouragement come too easily

EXPLANATIONS FOR PATIENTS ON REDUCING DIETS

Less food is furnished by the suggested diets than the individual needs for maintenance so that exces sive body fat will be utilized In order to make this procedure safe for health it is necessary that the foods listed be eaten in the portions given Diets are provided for different types of individuals, use only the one directed An alternate menu for the 1 200 calory diet is included for the use of those who must economize Substitution of more milk and potato for fruits and part of the meat leaves the diet safe for continued use

Variety is secured by choosing on different days the various vegetables and fruits When three portions'

ing excess weight The essence of reducing is therefore to eat less and exercise more Some schemes have measured food intake, some exercise, and the best schemes both

The success which will be attained in reducing excess weight is in proportion to the accuracy with which the patient will obey instructions Definiteness of prescription is important Therefore the physician must write a diet prescription calling for a certain amount of calories daily, to be secured from a measured amount of protein, carbohydrate and fat. This is much like the handling of diabetes, except that the leeway given the patient for variation is greater

The great majority of patients can be reduced satisfactorily by the use of a 1,200 calory diet This daily total allows of plenty of bulk to satisfy hunger, plenty of protein for maintenance (at least 50 Gm), plenty of carbohydrate to avoid ketosis (about 125 Gm) and adequate amounts of minerals and vitamins The diet can be made appetizing With a diet at this level planned by a dietitian who appreciates tastes as well as food values patients are often surprised at the amounts of food they may eat

For patients whose optimum weight is over 150 lb , it may be wiser to use a 1,500 calory diet with 75 Gm of protein Such a diet is preferable for rapidly growing children and for pregnant women There are some patients with stubborn obesity in spite of honest and intelligent endeavor to follow the diet This is particularly a problem when exercise is limited For such patients, a diet of approximately 900 calories is use

Walk outdoors .. miles each day After four days, increase the daily walk by adding miles more each day until walking miles each day Increase the speed of walking gradually Keep a record of the weight weekly

ACCESSORY FACTORS IN WEIGHT REDUCTION

As accessory factors in a reduction diet program it is at times important to use iron to combat mild secondary anemia The diets reproduced here do not lead to anemia but will not furnish therapeutic amounts of iron The supply of fat soluble vitamins is difficult to measure or predict In case of any doubt it would be wise to prescribe along with a diet limited in fat the use of a concentrate of vitamins A and D, of which one of the least expensive is halibut liver oil The calory value of the oil can be ignored for this purpose The water soluble vitamins are probably furnished in adequate amounts by the diets They may of course be added if there is a therapeutic problem in addition to obesity, or if there is any reason to question the adequacy of water-soluble vitamin content of the diet

The wisdom of *thyroid therapy* to accelerate the loss of weight has been debated Certainly it is unwise unless the patient can be supervised closely enough to prevent development of thyrotoxic symptoms (See Chapter 5 for further details) Basal metabolism tests, careful observation of basal pulse rate and watch for tremors sweating and nervous irritability must be part of the clinical check imposed on any obese patient

of vegetables are mentioned, it is understood that all three portions may be taken of any one vegetable, if two or three vegetables are available, one portion may be served from each, to increase the variety Vegetables should be served without cream sauce or butter other than that listed in the diet

Fruits should be fresh or those which are canned without sugar No sugar should be added to fresh fruits in cooking them

Vegetables and fruits may be taken as salads if desired Vinegar or salad dressing made with mineral oil may be used

Buttermilk may be used instead of sweet milk if preferred Whole wheat bread is preferable to white or rye bread, bran bread should not be used unless by special direction The bread may be toasted if desired Sugar-free gelatin may be used, "D-Zerta" is such a preparation In any meal, tea, coffee consomme or broth containing no fat may be used in any amount desired

"Dinner' and "supper" may be reversed and served as "lunch" and "dinner' if preferred If hunger is annoying in midmorning, afternoon or evening, part of any one of these meals may be eaten as a lunch at this time (and, of course, subtracted from the meals for that day)

Water may be taken freely at all times, including meals, provided it is not used to refresh the appetite and thus increase the amount of food eaten In other words, chew the food and swallow it before drinking

Take some sort of exercise regularly each day

Use of special exercises to reduce weight at specified regions is at best a questionable procedure The major problem with exercise is to increase the total output of energy at the expense of the excess body fat We are still in ignorance of the factors controlling the localization of fat deposits in some types of obesity, in which deposits about abdomen and thighs are unsightly and disabling

who is to be allowed the use of thyroid The dose will have to be adjusted by trial and should start with 0 065 Gm (1 gr) tablets of U S P thyroid as a maximum for the first six weeks In some patients, obesity is lost slowly except on the use of thyroid with the diet, even though they have normal basal metabolism and no other evidence of hypothyroidism Such individuals seldom adhere rigidly to a limited diet, and it is difficult to draw any conclusions about them Occasionally these patients may tolerate large daily doses of 0 3 to 0 65 Gm (5-10 gr) of U S P thyroid daily It is usual to find that thyroid medication is ineffective in accomplishing weight reduction

The use of dinitrophenol should be discouraged with firmness, since it has caused too many toxic manifestations of varied types This drug does not belong in the list for human therapy

Patients often need to be warned about the nostrums for obesity too easily available in retail drug stores Some of these are inert Others are known to contain unstandardized amounts of thyroid, which is obviously unwise A significant group contains saline purgatives These will interfere with food absorption but may lead to the cathartic habit or other damage to the intestinal tract The use of bath salts, if effective in changing weight, does so by elimination of water through the skin This is so obviously a temporary expedient that its futility should be apparent Some reducing nostrums have been shown to contain the encysted ova of tapeworms which would serve to achieve reduction by producing parasitism

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